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AN ESSAY ON MEDICAL RELATIONS

JEAN M. STEVENSON, M.D., CINCINNATI, OHIO

(From the Department of Surgery, University of Cincinnati College of Medicine and the Cincinnati General Hospital)

NEVER before in history have there been such fathomless abysses between the opinions of men and such mulish resistance to getting around them by compromise. Strangely enough, there is one thought to which nearly everyone will agree. It is that the world is in chaos.

What conditions, what elements, what ambitions of men have thrown us into this dreadful crisis are now a matter of record. It will do us no good to dwell upon them here. The structure of a peaceful civilization is in shambles; no wishful thinking, no finger-pointing, no revelations of prophesies made since 1945 or 1932 or 1918 can restore what seemed so good, so strong, and so important to us in the past.

It is not quite accurate to say that we are in the midst of a single world revolution because we are actually in the early stages of many revolutions. There are social revolutions, political revolutions, racial and religious revolutions, all of which are taken seriously and are found to be intimately related in a continuation of three international wars. Why these have been given Roman numerals is not clear, because the first was neither won nor lost; the second never ended with a declaration of peace; and a third has begun without any official announcement.

On the basis of total participation of nations, actually there has never been a total world war because the big nations, self-opinionated as they are, cannot penetrate the shadows of their greatness to perceive the little ones who manage to stay out of danger and reap some benefits with the passage of time.

It is true that the pattern has changed but little through the centuries. Disputes between leaders of influence and trade are no more satisfactorily settled now than they were in the past with clubs and arrows.

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Lives of individuals and their governments have now become so complex that their affairs must be turned over to experts for management. These in turn, equally confused, seek advice from other experts who seem never to be found because they actually do not exist. The problems are so new and so immense that rules have never been formulated to solve them.

There are great revolutions here at home, too. We have them in transportation, communications, farming, mining, industry, education, engineering, medicine, and in many other fields of endeavor. Much of our restlessness, our rudderless floundering to get ahead, has resulted from the loss of a common goal through our inability to keep pace with, and our failure to adapt ourselves to, the products of our research in all these fields of endeavor.

We have progressed and we have prospered. Our standards of living are high, but our successes are being displayed rather badly. In brief, we tend to show poor breeding and careless training. We seem not to be proud of what we have accomplished. We show considerable indifference to the freedoms which have made such progress possible. We abandon thrift in failing to preserve great things already done. We often look upon our past with disrespect and take our future for granted. We squander our natural resources, and, instead of using a wise economy, we prefer to depend upon the development of synthetic substitutes against shortages. Frequently, engagements and promises are made freely with little consideration for punctuality and no great concern if they go entirely unobserved. Living in debt through spending for prosperity has spread from a national practice to a household fad. Gaining through practices of legalized dishonesty, the policies of "beating the rap," and "getting by with minimum effort" have become the popular and smart things to do. Shorter hours and more pay are inseparable phrases and are forced upon us as a fair exchange for less work of poorer quality.

These observations are so familiar that some become annoyed, depressed, or even enraged upon hearing them again and again. They are reviewed here merely to bring out the fact that the great social and political changes which are going on are the results and not the causes of our insincerity, our indifference, our loss of integrity. We should not ignore the charges and then quickly look for faults in others because everyone in America is in some degree to blame for what is happening.

We are losing our individuality! It is difficult to stick to moral principles when to do so means more work is involved, credit is likely to go to someone else, financial remuneration may be lower, or one is likely to have a dull time from the point of view of pleasure. It is so much easier to lose one's identity and responsibilities in a crowd where there is no need for worry about one's deficiencies or security. The group provides protection; a few leaders will do the thinking for the rest. The larger the group, the greater the bargaining power; and if it is large enough, it can trample all obstacles and never admit a mistake.

As individuals, we Americans have not grown or developed along with the nation. As individuals we are content to be counted as signatures on petitions,

testimonials for advertisements, stub-holders for contests, and as votes for politicians, who, although some of them are qualified for their jobs through experience and special training, generally look upon us as a mass, in which they think there is not one with the ability to take the office-holder's place and do a better job than he.

Fortunately, we have preserved the freedom which permitted Lincoln to do the things he did. During the war years of his presidency, he had problems in dealing with pressure groups which were quite similar to those that are prevalent today. Troubles within his cabinet were even greater and yet he mastered his job because he based his decisions on his belief in humanity and a sense of fair play between men for the good of the country. Such men are rarely found at the head of a nation. If they are self-made, their aggression usually tricks them into losing the qualities of Lincoln before the post is reached. If they are advanced through political favor, they are managed by political advisers about whom little is known; and what is more important, these advisers are never selected by vote of the people, and do not have to answer to the public for their mistakes and their treachery.

It is difficult to see how we could have been hoodwinked and cheated until it is realized that we Americans are a trusting lot and expect to get the best out of men without bothering to check as to whether we are getting the full measure due us. We make public loans without collateral. We hire teachers without listening to their lectures. We place representatives in government without bothering to acquaint ourselves with their qualifications before election or their performance after election. We thrive on half-truths and thus are easily prepared for gossip. We have been trained to pay our money down on the advice of salesmen who do not necessarily need to know about their products but who are masters at misrepresenting the facts in an artistic and convincing manner.

Since it is impossible for us to develop such a storehouse of knowledge that we will always make the right decision without help, we do have to depend on the advice of others many times every day. Our ultimate protection lies in our follow-up on good and bad advice. It is time to re-establish the demand for undiluted truth and an unwavering penalty for those whose acts have deviated from an honorable course.

Many of our half-truths are gathered from distorted headlines, early editions, and radio scoops. Too few read the editorial columns and cover the weekly digests of news after it has had time to mature and thus reveal its full meaning. If this were done as faithfully as radio audiences follow their favorite programs of continued stories, it would not be long before the bulk of our adult population would be equipped with the same knowledge of domestic and world problems as is held by our representatives in government. The public would be in position to judge for itself and there would be good prospects for separating the propaganda salesmen from good men who are trying to give us an honest account of the developments in news.

We are learning, but the process is slow, and the price is costly. We voted for Harding because he was a Republican; scandal rode in with him. We brought

in Roosevelt and the New Deal because the Democrats said Mr. Hoover caused the depression. How fortunate it is that he has lived to see us change our minds about that notion.

We continued with the New Deal because the gangsters of prohibition days showed us the effectiveness of organized minority groups having for a common purpose the complete control of large numbers of people for political and financial gain. We know the pattern now. And even though we may think as individuals, our public actions must conform to group policies. Let an individual speak of reforms and principles contrary to custom and he may be torn apart in the press, and in the courts if suit is brought against him. But provide him with an impressive following and it is certain that he will be treated as a man of influence.

As individuals, we are cognizant of what has been taking place about us. We are aware that certain walls have weakened and are about to topple. As professional men, we have had to submit our opinions to the changes of the times which have bearing upon our nonprofessional lives. We have seen the need for organization to protect the kind of lives we wish for ourselves and our families. The point is how shall we do it?

It seems to me that there are two distinct phases of the problem which require divided attention. One has to do with the nonprofessional portion of our lives. In this our interests are exactly those of all other Americans. It has to do with how we live; where we live; from whom we buy our insurance; how and where we educate our children; the churches we attend; the traveling we do; the vacations we take; the taxes we pay; the security of our children, our investments, and of ourselves when we can no longer work. And incidentally, we are interested in the preservation of our democratic form of government with restoration of a program of economy, of reward for a full day's work, of respect for the truth, of punishment for dishonesty, and the continuation of national improvements for the good of the people without the use of doles.

This calls for more activity than going to the polls on election days. Considering our group of professional men as a whole, it would be difficult to find another to match it for years spent in competitive, selective, scholastic training, or one to come near it for the wide experiences and basic understanding of man's social, physical, and humanitarian needs. Unfortunately, we have shown no interest at all in government until it begins to design restrictions upon our own privileges. Excluding the Public Health Service, which is really a professional agency, rarely do we seek representation in a governmental body of higher level than the local school board. Our aim would not be to load governing bodies or to control them for the passage of legislation beneficial to our profession; but rather to improve government by providing a useful representation of a source of material gained from first-hand knowledge of thousands of individuals—their thoughts, beliefs, their problems, and their needs. It is a new idea. It is something totally lacking in government at the present time because no one but a doctor can know so much about so many, and doctors have taken little active part in government thus far.

The plan would require careful preparation. Aid could be given, and experience could be gained through work in local, city, and county governments. In time, our more influential men could be advanced into the state governments and finally to the legislative bodies in Washington. It would be a way to contribute something toward the correction of certain social evils which are unrelated to our own inability to provide an even spread of professional services throughout the population. To do this requires consideration of the second part of an organized plan which deals with the professional aspect of our lives.

This review of social trends was required because there has come a critical phase in our profession's life, the outcome of which is going to be decided by the influences of these very same evolutionary trends in society. The isolated lives we have led, aloof to all trials beyond our daily tasks of looking after the physical ills of the members of our communities, are over. We not only must widen our sphere of influence as men, but we must quickly broaden our views on the medical program as a whole, evaluate the responsibilities and power of the Medical Association, and take inventory of the effectiveness of the tactics in education now employed in our undergraduate and graduate schools of medicine.

When it comes to us from many sources that there is something wrong with our medical service, it is reasonable to assume that there must be some good reason for complaint. Ill feeling can be aroused in an argument when clear proof is not forthcoming. To say that we have the highest medical standards and provide the best services of all times in our history or that of any other country is a bit of an echo. We say it and it comes back to us. The progress we have made is relative only. We started with a base line pretty close to zero shortly before the turn of the century. We have made technical improvements, but even so, much of our advancement has been made possible through the brilliant discoveries and inventions of chemists, physicists, engineers, biologists, bacteriologists, and others who were not or are not doctors of medicine. They have handed valuable agents to us for use. We use them, forget our indebtedness, and say, "Look at our results. We are wonderful. The American public is lucky to be under our care." Then we compare ourselves with our European neighbors, who were far ahead of us until all organized progress was disrupted by the consequences of two wars. No fair comparison can be made, and we have no reason to be complacent about our present position.

It is generally believed among surgeons that the technique of surgery is no longer advancing. We are attacking new fields but our techniques are fundamentally unchanged. Our successes are largely made possible through the adjuvants provided us.

Our medical specialists fare no better. It is unlikely that they are smarter men than they used to be. The fact that their bags contain more tricks is the only real difference. The history and physical examination lead to an even longer list of impressions, and then the patient is subjected to a series of tests by hosts of technicians and consultants until abnormalities are found. In nonsurgical cases, the treatment will fit into one or more of roughly five categories: diet, sedation, blood tonic, hormone therapy and/or antibiotics, while the patient is observed for improvement.

This simplified version of medical progress removes a little of the mysterious glamour customarily associated with it. There is little wrong with the present-day approach to medical diagnosis and treatment. It is made according to scientific rules and requires great skill and knowledge, but so does the planning for the wiring and fittings of the instrument board on a B-36 bomber or the chemistry of an atomic explosive. There is no justification for conceit about our place in the social order. We owe so much to other allied professions that the glory of achievement and service can scarcely be claimed as entirely our own. There is no doubt that adjustments to change will have to be made by us.

As to the matter of the growing belief that there is a shortage of doctors, I am afraid that it won't do just to ignore the question, or answer it in a back-handed way by talking about the high cost of educating and training a doctor, and about limitations in the use of expensive medical institutions and equipment.

If we did make such a reply, we would be sincere and correct. We should repeat it often and add to it statistical proof of medical progress in the last fifty years. We should include in it the record made by the Medical Corps in the recent war. And we should make it clear that the thousands of medical officers highly skilled and trained in the essential specialties were made available through civilian institutions financed by state, municipal, or endowment funds, involving a system of long and careful training over many years in a peaceful country for peacetime service to its countrymen. It was done without federal funds and the men were ready for the nation's call to emergency service regardless of age, family, institutional affiliations, and practice, and even, in many instances, physical handicaps. They took with them and applied the same drugs, remedies, and techniques that were developed in the institutions within a capitalistic country of free enterprise and were used in everyday work at home. Beyond the regimentation of these forces, the government and military services can lay no claims to the performance. It was strictly the result of independent civilian enterprise. What skill and knowledge they took with them, they also brought home. In no sense was their part in the conflict a special preparation for war such as was made in the expenditure of billions for tanks, guns, and planes in rapid production. There was no possible way to duplicate by assembly-line methods, at any amount of public expense, all these men had to offer.

And after it was over, the regimentaries failed to profit, by study and organization for future use, that which had been experienced and was still fresh in mind. It has been lost like the fighting equipment which was left in the field to be picked up by the friends of the enemy. For example, the non-military part of the adult population has not benefited even by as much as a suggestion that active immunization by tetanus toxoid might be a good safety measure for them, come peace or war.

Yes, we can and will say all these things to the public and more. They will believe them because they are true. They recognize the very fine care that American doctors can give them and will want it all the more. Because of geographic location, insufficient funds, overcrowded hospitals and offices, long

hours and even days of waiting, which may delay or deny them proper medical care, they will resort to the same methods of procurement that they used for obtaining wage contracts, farm subsidies, security benefits, and so on. They will accept service of a lower quality to get service at all. The public cost of federalized medicine is no concern to nontaxpaying citizens or to many others who seem to show no qualms about the mounting public debt since 1932.

Although the criticisms which are made about our services have to do mainly with the belief in an actual shortage of doctors, the entire attack can be separated into three main complaints.

The first, of course, is the apparent shortage of doctors. The second is the shortage of hospital beds; and the third is the over-all high cost of medical care.

Any and all criticisms are directed to the doctors in general and the Medical Association in particular. It is assumed that since it requires doctors to train men to become doctors, any shortage in graduates is entirely due to the doctors themselves. It is believed that we can control the flow as simply as regulating the faucet on a water pipe and that we do it to hold down our numbers to avoid competition and a lowering of prices according to the rule of supply and demand. Impetus to the belief has been gained by the manner in which the schools of arts and sciences brought more chairs into the lecture halls to accommodate the enrollment expanded by the war veterans. The difference in the type of training required for these students and that for medical students seems to be hard for the critics to comprehend. They proceed on the theory that a doctor is a doctor. What happened to him in medical school and the amount of graduate training he has had after graduation is beside the point. Whether the man is good, bad, or otherwise does not count. It is the license to practice that matters. The military services used this theory during the recent war.

This attitude toward the training of doctors is dangerous because, if adopted, it would force many doctors against their will into doing work they are not qualified to do and cause patients to go to sources for treatments that they would prefer to get elsewhere. However, the practice is a standard procedure in plans for socialization.

So in our public relations we must get across the point that the medical profession has learned many things during its years of development. It carries a responsibility greater than that of any other profession or occupation on earth. Since it has accepted its responsibility and has established a goal as close to scientific perfection as it is possible to achieve by training men, over long tedious years, for one specific job and duty to mankind, it cannot afford to be mixed up with political whims and regulations. Our record has been the result of our ideas and our efforts, with financial assistance from the public. We have confined our efforts strictly to our field of endeavor and we have never deviated in our belief that it is our duty to select the most competent candidates for training, to restrict their practices until they are trained, to qualify them for specific duties, to keep them informed, and to maintain their skills after formal training has ceased in order for them to perform their duties to the best of their abilities to the advantage of all humanity. It should be clear that until

politicians can do as much for our government and its subjects, they do not measure up to the specifications for taking over the management of a work such as ours. And furthermore, it should be emphasized that it is a criminal insult to use the services of our profession as a bait to be dangled before the public for the re-election of politicians to perpetuate their selfish, scandalous, traitorous interests at the expense of humanity.

In the review of our public relations, we must not lose sight of these facts. We had 160 medical schools in 1905 and graduated approximately the same number as we do now with seventy-nine schools. The capacities of the 160 schools would have permitted a much larger enrollment than they had. It was a matter of too few applicants, resulting from more rigid entrance requirements, more strenuous courses of instruction, and stiffer licensing examinations set up as a response to the consistent effort on the part of the American Medical Association to improve standards of medical education which caused twenty-nine schools to close in the following five years and caused seventy-five schools to close by 1920. The law of supply and demand worked here well enough. I would not be surprised if the possibilities of practicing for a fee and lecturing for a fee weren't responsible for the great number of schools in existence at the end of the century. With the elevation of standards this appeal disappeared and the diploma mills ceased to exist. It has been a long pull uphill since those days and I believe there will be plenty of objections voiced within the profession against running off batches of premature doctors for use in war or peace.

It must be explained to our public that the present number of medical schools was not determined by the doctors or the Medical Association. It was a result of natural causes. Some of the causes for elimination I have mentioned. Others would be that the medical college of a university often costs as much to run as several other colleges put together. Most institutions could not afford to start new ones. Hospital affiliations were not available to others, and some institutions were located in such small communities that clinical material for teaching purposes was not to be found at all.

Now that rising costs have threatened the existence of many of the old institutions which did survive, we find that the type and duration of medical training are even under question. Since the problem involves numbers, space, time, and cost, the idea would be to get more in the same space for shorter time without increasing the cost. The formula has been borrowed from industry. We are to roll the metal thinner, put on less paint, substitute plastics and cheaper metals for precious steel. The materials will go farther and we will have more units for use. Undoubtedly, this stretch-out can be applied to a limited extent. But the time factor is completely out. Only by careful trimming of certain branches of training are we able to make room to teach new courses which have to be added to the curriculum. The space factor has a tiny bit of merit. If each school were to accommodate a few more students in each class, the total graduates for the country might be increased by a few hundred for the year. It would help, but it would still be far short of satisfying the demand.

The use of a quarter system or a trimester system with a year-around schedule is already in effect in some institutions and is contemplated in others to gain another year which is to be added to the present course of training. It will not become the solution for training more doctors.

Since we cannot account for all the factors which left us with our present number of medical schools dating back to conditions twenty to twenty-five years ago, we should not overlook the possibility that in the changes of the times the demands made upon our services now and the methods by which we provide them may be completely out of proportion to the doctor-population ratio of twenty-five years ago. This should be investigated before we become vehement against proposed expansions in our present educational facilities. Here are some vital statistics.

In 1925, when the eighty medical schools graduated 3,974 doctors, the country had a population of about 114,000,000. This was a ratio of one graduate to about every 28,700 people.

In 1939, when 5,089 doctors were graduated, the population had grown to 131,000,000. The ratio of graduates to population had improved to one for 25,700.

In 1949 the number of medical graduates for the year amounted to 5,095. This was an increase of only six over the number for 1939. While the population had increased to 154,000,000, the ratio of graduates to population had lowered to one in every 30,200. The chief point of significance here is that for the last ten years we have only slightly increased the number of doctors graduating each year while there has been a 17 per cent increase in the population.

Such a comparison can be very misleading. Whereas we compare an absolute increase in population on the one hand with a relative increase in medical graduates on the other, it is the total number of doctors at the various stages of comparison in which we are interested. Actually the graduating classes of more than 5,000 represent an annual increase of nearly 3,000 over losses from death and retirement. In this respect the total number of doctors has been said to be increasing more rapidly than the population.[1] This view is not shared by the Surgeon General of the United States Public Health Service, who reported that if the present rate of training of doctors continues, there will be a shortage of 30,000 by 1960.

An entirely different approach was voiced in a meeting of the American Conference of Academic Deans in January of 1950. A committee appointed to study the problem of admissions of students to the medical colleges struck fire in the meeting with accusations based on a one-out-of-four ratio of acceptance of candidates, all of whom had been prepared for starting medical training.

The debate will go on as each presents the problems closest to him. The academic deans did not seek advice from the Medical Association on the country's needs, but fell in with the popular belief because they were stuck with 18,613 premedical students without an opportunity for continuing their medical training. It represented a lot of wasted effort and finances on the part of many individuals. The profession undoubtedly was deprived of many good men in

those rejected and it also created many enemies in the same men, their relatives, friends, and teachers. Apparently the regulation of trainees will have to be extended into the premedical period as well. Perhaps this situation could be improved if the academic deans and the deans of the medical colleges were to meet for a discussion of the problem.

Obviously, the United States Public Health Service has plans for a great many more doctors, the academic deans have too many students in premedical training, while in the New York area the population is pretty well saturated with doctors from the graduates of several local schools, the recent immigration of doctors from Europe, and the many attractions of the metropolitan area. This is shown in the doctor-population ratio. For the United States in 1947 the ratio was 1:719. For the state of New York it was 1:511. For New York City it was 1:410. The figures are impressive when compared with the prewar ratios of England, Germany, and France, which were 1:1,490; 1:1,560; and 1:1,690, respectively.

We must look for the merits in all reports, but be very careful with the doctor-patient ratios. So many important facts are concealed in such comparisons. In Europe, where resident systems are not developed along the lines or to the extent that they are in America, doctors do not confine themselves as rigidly to specialties as they do here. One broadly trained physician in the 1:1,500 ratio might be able to give better emergency service to his territory than three doctors in the United States in a 1:500 ratio if the three were composed of perhaps a neurologist, an allergist, and a psychiatrist. With all credit due these specialists and their work, they do not deliver babies, fix broken bones, treat infections, and handle the ordinary surgical problems which fall in the line of duty of the well-founded community doctor. It is in this that we find the reasons to account for the complaints from the public. We speak of a high doctor-patient ratio in American medicine, but in terms of public service it may not be entirely true.

In the early history of American medicine the brief medical course which emphasized didactic lecture and bedside study of patients, but offered little or no opportunity to approach the problems by laboratory method, was given to students who were not required to have any basic training in science, or college training in any form. This method of instruction naturally succeeded in training large numbers of men who could do nothing but general practice. It failed to teach the scientific approach to diagnosis and therapy and therefore created little curiosity along these lines. Progress in research, diagnosis, therapy, and teaching was scarcely possible until men with natural ability, drive, and more than usual college preparation started to go abroad to participate in the more advanced courses for graduate and postgraduate training. The movement for specialization began with the recognition of these men for their uncommon skills, and it has been continued through the teachings of those they have trained. An even pace in the development of new ideas could be maintained between medicine and the related sciences. The advantages of a complete medical unit such as the hospital or clinic with or without affiliation with a University were soon apparent

to everyone. The patients flocked to the medical centers either on their own or by reference on the part of the family doctor. Many of the doctors sought post-graduate training, never to return in their former capacities of general practitioner.

Students trained under such a system likewise were impressed and fascinated by the work. They found that they could not leave the medical centers because they could not work alone. They were dependent on the advantages and service provided by hospitals, laboratories, universities, and their trained personnel. To settle in a community where these were not available meant that they could not continue their work as they had been trained to do it. They were in competition with practitioners already there, trying to do the work of the specialists as well as their own. New men could not subsist without the aid of references of patients from others, and they could not get cooperation in starting a unit along the lines which they had been trained to use, when such units would largely absorb what the practitioners were doing independently. Smaller communities which are so remote and scattered that they can neither attract nor support a practitioner surely cannot be expected to hold a specialist.

And so, with medical progress, medical standards, medical research, diagnosis, therapy, and teaching all owing their excellence to the concentration of thought, effort, and skill on the part of men who have specialized in their training, it appears to be utterly stupid to spoil that which we have already developed, and to which we owe so much, by flooding the country with doctors who have been intentionally poorly trained so that they can do nothing else but retire to the bush to practice an inferior brand of medicine to the detriment of themselves, their patients, their profession, and their country. A double code of ethics has never worked in any high enterprise. In medicine the training must be uniformly good. We cannot afford to cut corners, and shorten the course for the purpose of increasing the numbers. Under any plan we should not increase the numbers until we are in a position to provide opportunities for nearly all of them to equip themselves in the line of work for which they are best fitted and want to do. I have in mind the continued development of our residency system of training so that both the system of training and the medical service designed to meet the country's needs can be supplied at the same time.

First of all, as I have pointed out in the early part of this discussion, let us be consistent with our belief in unity of purpose for perfection in service and make up our minds to give the country what it needs instead of that which different ones may think would satisfy the people at the moment. This would certainly be in contrast to the politician's method, but it would avoid constant changes, wasteful indecisions, and would provide a goal toward which everyone could watch us proceed.

With the improvements of the highways throughout the country, of all forms of transportation and communications, and with the electrification of the rural communities, the advantages and attractions of both country and city can easily be shared by inhabitants in either area. The congregation of individuals for educational purposes, work, and recreation, with the daily trip

to and from home, has been extremely successful. It is so satisfactory that industry has been moving into the country to escape city restrictions and congestion. With this trend few will disagree.

Most people will agree that the complete hospital or clinic unit, that is, one with ample beds, laboratories, outpatient facilities, and personnel to serve the area, constitutes the most ideal arrangement for doing the best job in providing emergency and elective care to patients. Surely we will not find many that will argue that the home is the better place to keep the acutely ill patient or to treat the minor ailment of an individual who is perfectly capable of being ambulatory. Since we can assume that doctors need and prefer to have special institutions in which to carry on their best work, and patients have come to accept the institutions as the acme of perfection in providing everything that is new and good for them, there is no reasonable substitute forthcoming to stop us from adopting such units and extending them to the frontiers for this very purpose.

Now to consider some practical aspects: The location of these units would be determined by population densities; water, power, highway and railroad facilities; urban accommodations for the personnel; and by the distance from already existing hospital facilities.

The size of such units would vary considerably but would never be small. The role of such a unit in the proposed plan is a double one. Its service to the patients has been expressed. The patient's service to the doctors has not been discussed. The units must be of such size that some would provide training for medical students, and nearly all would provide training for internes and graduate students in resident systems of training in most of the specialties. The capacity should not be less than 500 and should be more if the population can carry it. Only in sparsely settled districts, where distances are great and a satisfactory patient load would be impossible to get, would the units be dropped to a size which would be impractical for a full teaching program.

The program would discourage the expansion of small hospitals in small towns which are burdened with a load in running them and have never realized the full benefit of complete hospital service to everyone in the community. Such small institutions need not be abandoned but may be converted to convalescent homes, tuberculosis sanitariums, maternity hospitals, psychiatric hospitals, or, if preferred, continued as private hospitals for general admission.

The new units would be built with funds appropriated by Federal and State governments, governments of counties, and, possibly, municipalities in the areas, and would be administered by the agencies that built them.

The professional care would be strictly outside the jurisdiction of the housekeeping administration. The professional administration would be under the direction of the faculty representatives of the departments of the regional medical school. Privileges of part-time practice would be granted to help defer the cost of university employment, but full responsibility for research, graduate teaching, and local medical programs for the professional men would be maintained. Whenever possible, local men would be employed in the teaching program.

The units would provide living quarters for the resident staff, offices and equipment for rental to members of the staff and the professional men in the community, if they chose to use them. A large outpatient department would be planned for ambulatory patients. Ambulance service would be available. An assembly hall and library to accommodate the local requirements would also be included. The cost of the service would be aided by an extensive insurance program conducted along the lines advocated by the Medical Association. It would not be compulsory, but would be available to all.

The unit would be a combination of the private hospital and the general hospital as we know them at the present time. The patients would have similar privileges and management. Indigent patients without insurance, or with hospital insurance and no professional insurance, would be under the management of the resident staff and under the supervision of the teaching staff. No patient capable of transportation in the geographical area would be denied hospital service. When necessary, home calls would still be made by men in practice. For indigent cases, the service could be arranged by members of the resident staffs or by the visiting nurse, when patients could not be moved.

The plan is not impractical or impossible because it is drawn according to the present-day methods of operating many of the university hospitals represented in this Society. It goes far toward retaining medical education under the jurisdiction of the universities where it properly fits. It retains some of the cost of support for the individual patient and the community it serves. It protects the profession against political interference in dispatching its duties. It provides the best care for everyone within its geographic area. It brings to the practitioner the latest facilities for diagnosis and treatment, expert personnel for the care of his patients, and University extensions for continuation of study. It does not interfere with the conduct of his practice. It would stimulate the expansion of insurance programs in communities where patients would ordinarily fail to reap full benefit from such insurance. In brief, it would retain much of our present system of medical service and provide government aid without throwing the entire cost of support on funds derived from taxation as would be the case if socialization were to be developed in full. The voluntary insurance program does not allow, and thereby protects us from wasting time on, treatment of minor ailments of imaginary type which promote the tidal wave of patients seeking free service at government expense, as permitted under socialization.

Furthermore, in view of our confidence in and admiration for the resident system of training specialists, in view of the efforts made to bring the highest peak of performance to every residency in operation and every resident under training, in view of the demands of examining boards, the dearth of really good residency programs, and the great demands of candidates for them—in view of all these things we could at last offer them what they need, get what we want, expand enrollment in colleges, absorb more of the applicants from the arts and sciences, provide the additional doctors with proper training for the needs of the public without a catastrophic upheaval in the profession and the public treasury.

It can be planned expansion of services and may be strictly experimental at first. It would be accepted and successful under strong leadership having competent advisers with broad vision and determination for doing what is best for the profession and the people.

We have one organization to bargain for us and manage the program—The American Medical Association. We have one other to assist and give advice—The Association of American Medical Colleges. We have, to date, seventy-nine medical colleges to participate in the teaching program of expansion.

In recent years the American Medical Association has attracted nationwide attention. There has been little change in the Association itself, but there has been a change in the work it is doing and in the work it is believed to be capable of doing. We shall not take time to go into details of its accomplishments but merely say that, in the main, its work has been excellent and its contributions to medical education, medical practice, and public health have been greatly appreciated and accepted without serious controversy.

Nevertheless, as one moves about through little groups where doctors are gathered, one hears comments about the "medical situation" which reveals a very peculiar attitude which some men hold toward the Medical Association. Although they have accepted its decisions in professional matters as a liaison organization between the profession and the public, they do not look upon the Association as a liaison organization between the profession and the government. At the very moment they seem to be unwilling to trust the Association in this particular phase of the work, they actually look to it for the settlement of their problems, and at the same time are primed for criticism of nearly everything it plans to do.

What is the reason for this attitude? Since the American Medical Association is the only organization at present which incorporates doctors of all specialties in its membership and, in doing so, theoretically represents all doctors in every branch of the profession throughout the nation, it is the only organization that can officially represent the entire profession and be its official spokesman. If one reads through the constitution and by-laws of the Association, he will find sufficient machinery to enable it to accept the role of liaison organization between the profession and the government. Furthermore, decisions which are being made and policies which have been formulated by delegates and top officials of the Association are being interpreted by reporters and news writers as representative of the attitudes and wishes of the profession as a whole. Herein lies the beginning of the answer.

Actually, the rank and file doctors have not had any more to do with such matters than they have had with budgets and international policies in the federal government. While the members of the Association have been satisfied in the past to have ordinary matters concerning the profession handled according to the provisions in the constitution and by-laws, they are not ready to relinquish their rights to opinion, to suggestion, to approval or disapproval by vote on such matters pertaining to issues as important as federalized medicine.

Doctors are afraid that the wrong things may be done, or that not enough is being done to meet the needs of the country and they would appreciate having more to say about these matters.

There should be a way to encourage the submission of ideas by individuals, by county or constituent groups. These suggestions could be directed to appropriate committees for study and investigation. The better ones could be reported to the House of Delegates. It would be possible to integrate ideas into proposals or bills. After approval in the House, the proposal should be sent through channels downward to the county Societies for vote. The proposals might be accompanied by suitable explanatory remarks in a printed or recorded form. Such a plan would be almost a pure form of representative government and the referendum would come close to unifying the doctors on whatever plan is eventually adopted. At least everyone would have the satisfaction of having had a part in it.

In conclusion, there is still another relationship about which there has been such a great ado that it deserves a few general remarks. It concerns the doctor's relation to the students—both undergraduate and graduate. Although nearly all doctors should and do show a sort of fraternal interest in the problems, the welfare and the quality of the graduate and, indeed, the responsibility for whatever happens rest upon those of us who are employed by the schools to do the teaching. The quality of this relationship is often expressed in the popularity, the success or failure of a medical subject or a complete curriculum. Just how seriously this relationship has been abused is revealed in the very unstable state of the curriculum and our inability to reach an agreement on how and where it should be stabilized. This is not so much the matter of a difference of opinion between schools as it is between departments and personalities in any given school.

The topics of lectures rarely change from year to year, but what is worse, if they do, the contents of the lectures may not be improved. The students are now graded according to advancement in study, but when we shift dispensary services and ward assignments from junior year to senior year or senior year to junior year, and when the same or different lecturers discuss the same assigned topic, such as hernias, appendicitis, or cholecystitis, with students in the second, third, and fourth years of training, we are losing sight of gradation in training and are wasting valuable time in repetition.

In 1831, Drake[2] advocated a six-month school term. It required a quarter of a century for it to be adopted by a few institutions. Even in those days of a relatively limited knowledge about medical subjects, six months seemed a most necessary requirement for instilling the subject matter into the minds of the students. Today we are using his four-year program and have increased the term by only two months, in spite of the enormous expansion of the profession and the added training in diagnostic and therapeutic skills.

Further scrutiny of our eight-month term shows a two-week holiday for Christmas, a week or ten-day period for examinations at the end of each

semester, plus a few more days off for birthdays, Thanksgiving, election day, and so on. Time off is welcomed by all of us, but these deductions mean that the actual period for instructional guidance amounts to about seven months. Although, 120 years ago, Dr. Drake thought it would be expedient for the student to work on the hospital floors during the summer months, we have just begun to give serious consideration to the idea as a means of taking the pressure off the already crowded standard curriculum.

It is expected that when something worth while is accomplished through certain alterations in our system of teaching and the results are made known through publications and friendly exchange of ideas in conference, the changes will become popularized and will be adopted on their merits. Similarily, when a course becomes obsolete or unattractive through lack of effort, or poor instruction, it soon loses the student's support and the course is dropped or radically reduced as a requirement of importance. These are natural forces of control and are best applied by the local groups according to their own needs, rather than as a master plan in the form of a new curriculum to be installed in all institutions regardless of whether they need it or want it. Once again we are in a new phase of alterations and I am confident that differences will be settled through the old evolutionary forces and we shall scarcely be aware of the transition.

Departments have need of men of many qualifications. They have every right to select the individuals according to their needs. Investigative work must be done. Graduate instruction requires talented surgeons to share the long hours at the operating table with the young residents. The varied and strenuous duties of the professors make it mandatory that associates with initiative, resourcefulness, professional ability, and leadership be employed to help carry the load. But why should the primary purpose of a clinical department in relation to the medical schools usually be considered of secondary importance whenever a graduate school is in operation? If we are fair about it, the graduate and undergraduate students should have equal consideration. One frequently discovers that this is not the usual practice.

A successful chairman must be a good administrator. A successful administrator is one who has the ability to manage a complicated job by getting others to do most of the work for him. So the administrator seeks other subordinate administrators to carry out special assignments. As a general trend in many schools, one of the first to be delegated is the teaching schedule and the assignment of lectures. The plan is drawn up and the job is done. In order to divide the time, so that it will not be a burden to a few, everyone in the department is given classes to teach. They are often assigned without consultation with the instructors as to their best qualifications or desires in the assignments. When the program is once going, the classes are rarely visited by the professor or the one responsible for the teaching schedule. No one knows how well the work is being done, what is being taught, or how much is being repeated by other instructors in the same series. Students have been known to carry on open debates between instructors who have seen the same patients but have never met for the benefit of the students to settle their differences of opinions.

As for the dispensary work, few qualified men will regularly give up their time to take part in student instruction. If the clinic is held during morning hours, it interferes with operative schedules or hospital rounds. During the afternoon, there will be conflicts with office hours or research programs. We settle for any English-speaking, practicing doctor who is willing to visit the clinic with some degree of regularity for a half hour or so each week. In due time he is rewarded with a title in the university catalogue and thereafter may be seen less frequently.

There is a great tendency for lectures to become spontaneous expositions on personal experiences with no previous effort at organization of material or acquisition of teaching aids which would enhance the value of the lecture to the students. The busy doctor who teaches as a favor is pardoned for being late for a lecture or missing it entirely, and no apology is expected.

A few in every department will recognize these weaknesses and may have neither the time nor the privilege to do more than they are already doing. Eventually, a statement of dissatisfaction will reach the chairman. It is followed by revisions dispatched through the same channels, to the same instructors who change their hours, change their subjects, but do not change their habits or their results.

This state of affairs is not due to the work of incompetent men. It results from a lack of teaching enthusiasm due to the substitution of a greater interest in research, graduate teaching, or the application of a specialized skill. The only reward for good teaching is the satisfaction gained by the one who does it. If he obtains greater satisfaction in doing other work, teaching will hold less appeal for him. Besides, success in the other endeavors carries wider recognition and considerable prestige for the individual, the department, and the school.

If each of us in his own department would analyze his teaching effectiveness and do his best to always give a performance that would tax his capacity; if each would show tolerance, respect, and consideration for the judgments and skills of his colleagues and associates; if each would exemplify nothing but the conduct of a gentlemen in the presence of the patient and the student; if each demanded absolute honesty, respect for public property and public funds, and a sense of duty and service to others; if each would take the time to help the student, listen to his problems, take some part in his activities and become familiar with his thoughts, then all of us need have no fear of drastic changes in the curriculum and loss of hours allocated to our departments. Our graduates would not take up the cry about "rights to individuals" and yet say nothing about obligations to their patients, their school, and their country.

Social changes have made it paramount that we expand our medical relations. If our profession is to preserve its standards of excellence and its freedom, it must come forth with a program which will not only provide for the needs of the time, but one which will also apply to the demands to be created through future growth of the population and development of its government. The answer had better be good! And it must carry the approval of a majority

of the profession or it will not be accepted by the public or by the profession. The crisis we face has been growing for many years. A temporary solution can only provide us with a temporary peace. Whatever is eventually agreed upon will require the best from all of us, not from just a few.

In the meantime, a few thousand new doctors are being graduated every year. If we are sincere in what we believe should be preserved for years to come, it should be remembered that it is the additional time beyond that of a minimal requirement which we spend with our students that instills in them the ideals which we so anxiously hope to achieve and perpetuate through their effort.

REFERENCES

1. Rappleye, Willard A.: Comments Made at a Hearing Before the New York State Commission on the Need for a State University, J. A. Am. M. Coll. 23: 30, 1948.
2. Drake, Daniel: Practical Essays on Medical Education, Essay III, Cincinnati, 1832, Roff and Young, pp. 45-59.

STERILIZATION OF FROZEN ARTERIAL GRAFTS BY HIGH-VOLTAGE CATHODE-RAY IRRADIATION

IRVING A. MEEKER, JR., M.D., AND ROBERT E. GROSS, M.D., BOSTON, MASS.

(From the Surgical Research Laboratory, The Children's Medical Center, and the Department of Surgery of the Harvard Medical School)

IN RECENT years arterial segments obtained and stored aseptically have been transferred from one human being to another with a high degree of success,[3] and in the future there will probably be an increasing demand for arterial grafting, particularly in the fields of vascular, traumatic, and radical cancer surgery. It has been rather difficult to procure an adequate number of sterile arterial grafts, since there are relatively few autopsies on young human beings during which blood vessels can be removed aseptically within a few hours after death. In the effort to augment our present inconstant supply, which is limited by the need for rigid asepsis, it seems desirable to investigate methods by which contaminated vessels might possibly be sterilized without impairing their usefulness as grafts. If such a means could be found to kill bacteria without seriously injuring the vessel, there would be available from autopsies a large amount of material which could be utilized for grafting. In our laboratory, several methods for reaching this goal are under study. The present communication will be confined to a report of our attempts to sterilize contaminated aortic segments by exposure to high-voltage cathode-ray irradiation.

As is well known, x-rays are produced in a tube by driving electrons from a heated filament, accelerating them by an electromotive force ranging anywhere from 100,000 to more than a million volts, and directing this electron stream toward a metal target within the tube, so that a small percentage of the total energy is deflected off at an angle as a beam of x-rays. Cathode-ray machines are somewhat similar devices, but the entire electron stream is carried out of the tube (and not merely a small part of it deflected and transferred as is the case with x-ray apparatus). High-voltage cathode rays are beams composed of trillions of electrons, which are tremendously accelerated by a very high electromotive force; they have the power to penetrate organic matter to varying depths, depending on the voltage or energy employed.[7] Until recently, these electron beams could be produced only by unwieldy, gigantic, atom-smashing machines used by physicists for nuclear research. In 1939, Dr. John Trump of the Massachusetts Institute of Technology succeeded in greatly reducing the excessive size and cost of such apparatus so that it is now possible to fit one into a small room (Fig. 1) and still provide the same high-voltage cathode rays for research in the fields of cancer therapy and the sterilization of food and drugs.[8] By 1948 food sterilization experiments in the Department of Food Technology

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at the Massachusetts Institute of Technology had conclusively demonstrated its bactericidal action.[2] Apparently, the mechanism of bacterial death was similar to that caused by other types of irradiation[4] in that it depended on rays of fast-moving, electrically charged particles to score direct ionized bombardment of the genes and chromosomes, thus either preventing further reproduction or causing lethal mutations to occur in the microorganisms.

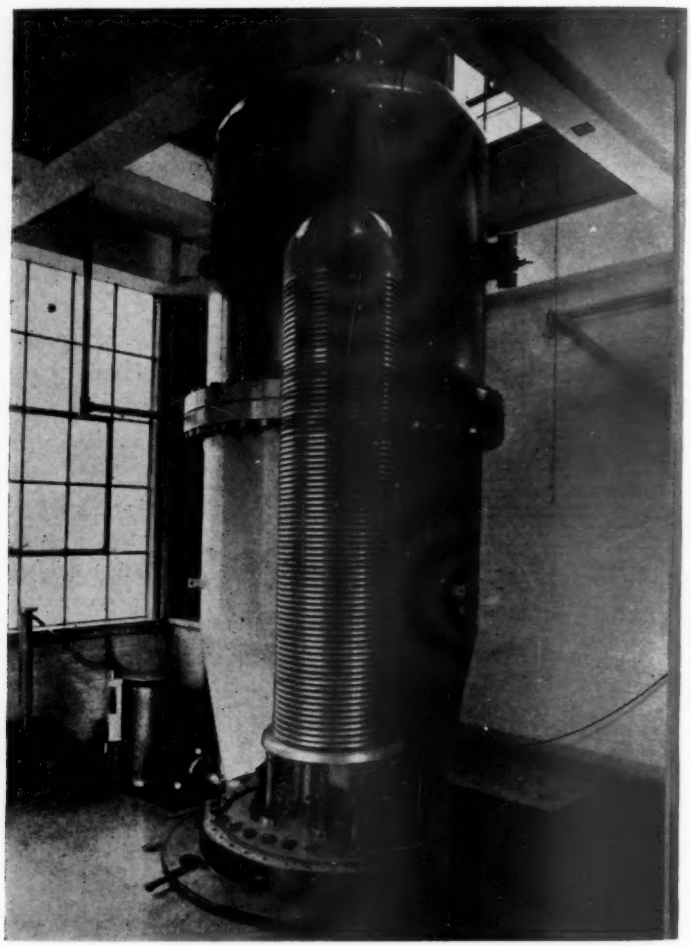

Fig. 1.—High-voltage cathode-ray machine. This photograph was made by 2 exposures, one with metal casing absent and the other with the casing in place. The central elongated tube is about 7 feet high. This is enclosed in the metal housing.

The cathode-ray machine at the Massachusetts Institute of Technology was made available to us through the kindness of Professor Trump.* This apparatus is arranged in such a way that it has beneath it an endless conveyor belt on which materials can be placed (even in a frozen state) and passed along through the electron beam, which is approximately 4 cm. in width. The accelerating force

*We are indebted to Mr. George E. Foley of the Children's Hospital for his supervision of the bacteriologic studies and to three men from the Massachusetts Institute of Technology: Professor Bernard S. Gould, who advised us on the types of irradiation most likely to prove fruitful in sterilization investigations, Dr. Samuel A. Goldblith who helped in the bacteriologic work, and Mr. Kenneth A. Wright, who carried out all of the irradiations.

comes from an electric potential of around 3.0 million volts. Radiation which is given off is measured in "Roentgen Equivalent Physical Units" (R. E. P.), this term being selected to indicate certain correlations between cathode rays and x-rays in their biologic effects on tissues. Because of the great power of the machine it is possible to deliver up to several million R. E. P. in a fraction of a minute.

Fig. 2.—Photograph of the electron beam (about 50 cm. in length). This beam is emitted into the room below the one shown in Fig. 1.

It was our hope that appropriate tests might show that cathode-ray irradiation of infected vascular segments would sterilize them without denaturing, degrading, or depolymerizing the organic vascular tissue to the serious degrees observed in all of the chemical methods of sterilization which we had previously tried.[5, 6]

As preliminary trials, portions of aortas were removed from 4 dogs (making no effort to keep them sterile during such removal). They were then irradiated at room temperature with 1.5 million R. E. P. and each segment was

then implanted as a graft into the aorta of a recipient dog. In every instance there was immediate failure because of intense reaction in the graft and occlusive thrombosis within a few weeks; we felt that these changes were dependent upon the damaging effects of the irradiation. It was therefore decided to try irradiation upon material in the frozen state, which was carried out in all of the experiments summarized in the remainder of this paper.

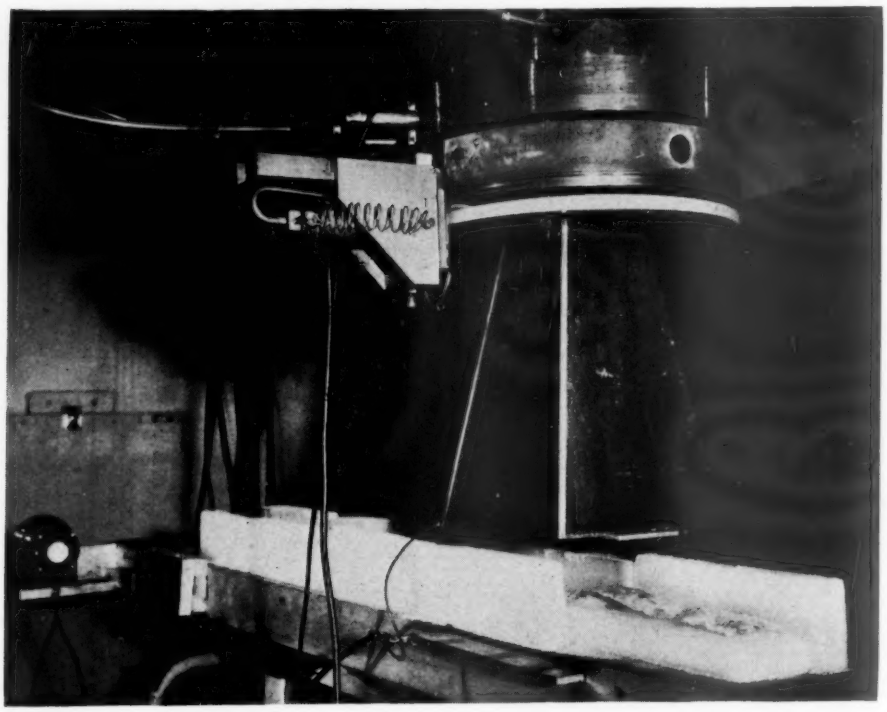

Fig. 3.—Arrangements for irradiation of frozen materials. The cone is around the electron beam. Below are blocks of carbon dioxide ice, carried along on a moving belt. Material to be irradiated rides along on these blocks of ice.

Three sets of studies were performed. First, segments of dogs' aortas were collected, intentionally contaminated with pathogenic organisms, irradiated, and then cultured, to determine the effectiveness of such irradiation in killing organisms. Second, segments of dogs' aortas were collected, frozen, irradiated, and subsequently implanted into recipient dogs to determine whether such irradiation would damage the arterial wall and thus impair its usefulness as a graft. Third, segments of dogs' aortas were collected, individually packaged in polyethylene bags, and frozen. Each bag was then injected with a suspension of living pathogenic bacteria, was then irradiated, and the aortic segment subsequently implanted into the abdominal aorta of a recipient dog as a graft. The dosages of the cathode-ray irradiation were varied from case to case so that we might determine what ranges would be necessary to kill organisms and yet not inflict serious damage on the graft wall.

Series 1. Freezing, Intentional Contamination, Irradiation, and Subsequent Culture of Arterial Segments.—To evaluate the effectiveness of high

voltage cathode-ray irradiation in sterilizing heavily contaminated material, the following experiments were done. One hundred and twenty-five segments of dogs' aortas were individually sealed in polyethylene bags, and frozen in a carbon dioxide ice refrigerator at –55° C. Into each bag was injected a few cubic centimeters of a suspension of eight different organisms. (Individual, 24 hour cultures were made of beta hemolytic streptococcus, alpha hemolytic streptococcus, *Staphylococcus aureus, Bacillus pyocyaneus, B. proteus, Escherichia coli, B. subtilus,* and *Monilia albicans.* These fluid cultures were then mixed together.) Within 3 or 4 hours each bag was irradiated in dosages varying from 1.5 to 6.0 million R. E. P. Within 2 hours after the irradiation, each segment was thawed and was cultured in beef heart broth for 7 days. There was growth from only 3 of the 125 cultures (one from tissue irradiated at 2.0 million, one at 3.0 million, and one at 5.0 million R. E. P.).

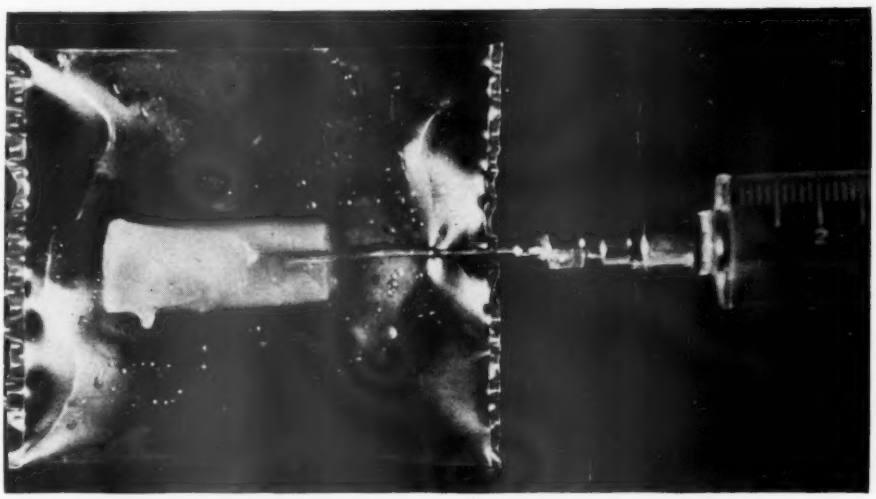

Fig. 4.—Frozen aortic segment in a sealed polyethylene bag being contaminated by innoculating it with a fluid mixture of viable bacteria (Series 1 and 3).

Series 2. Experiments With Irradiation of Nonsterile, Frozen, Aortic Segments Which Were Subsequently Used for Aortic Grafting.—Seventeen aortic segments were excised from donor dogs within 5 hours after the death of the animals, the removals being made without aseptic technique, so that obviously the vessels had some degree of contamination during such handling. The vessels were individually placed in polyethylene bags which were then sealed. They were frozen by placement and storage in a carbon dioxide ice refrigerator at –55° C. At some subsequent date all 17 of these frozen vessels were carried in a low-temperature thermos flask to the cathode-ray machine where they were exposed to 1.5 million R. E. P. (the minimum sterilizing dosage which had been recommended for foods). Such irradiation required but a few seconds. The vessels were then all kept in a frozen state in the carbon dioxide ice refrigerator from 1 to 5 months until each was implanted as a graft into the abdominal aorta of a recipient dog. All grafts were sutured in place, using a continuous

everting mattress stitch of 00000 Deknatel silk. The aortas had to be clamped off from 16 to 25 minutes during these operative procedures. There were no operative deaths. No anticoagulants or antibiotics were used after operation. No hind-leg paralysis occurred in any animal.

These dogs have all had excellent femoral artery pulsations for the periods of time they have been observed, some for more than one year. The results are summarized in Table I. Except for Dogs 1 and 13, in which the graft showed important degenerative changes, the irradiation had apparently produced little damage to aortic walls (Fig. 5); all of the segments had provided excellent aortic pathways.

TABLE I. SUMMARY OF SERIES NO. 2 EXPERIMENTS

DOG	SACRIFICED AT	CONDITION OF GRAFT
1	1 yr.	Considerable calcification; small mural thrombus (2.0 mm.)
2	1 yr.	Pliable, smooth, and excellent
3	6 mo.	Smooth, soft, and excellent
4	6 mo.	Smooth, soft, and excellent
5	6 mo.	Smooth, soft, and excellent
6	6 mo.	Smooth, soft, and excellent
7	6 mo.	Smooth, soft, and excellent
8	6 mo.	Smooth, soft, and excellent
9	6 mo.	Smooth, soft, and excellent
10	6 mo.	Smooth, soft, and excellent
11	6 mo.	Smooth, soft, and excellent
12	6 mo.	Smooth, soft, and excellent
13	6 mo.	Very satisfactory, except for a 2 to 3 mm. mural thrombus
14	4 mo.	Soft, smooth, and pliable
15	Still living at 4 mo.	Good femoral pulsations
16	Still living at 4 mo.	Good femoral pulsations
17	Still living at 4 mo.	Good femoral pulsations

Series 3. Intentional Heavy Bacterial Contamination of Frozen Aortic Segments, Irradiation of Them, and Use of the Segments as Aortic Grafts.— Forty-three aortic segments were obtained from dogs within 5 hours of the death of the animals. Each was enclosed in a sealed, airtight, polyethylene bag. About two-thirds were frozen by placing, and storing, them in a carbon dioxide ice refrigerator at –55° C. The remaining third were quick-frozen by immersing the bagged vessels in liquid nitrogen at –200° C. for 5 seconds and then transferring them to a carbon dioxide ice refrigerator for storage at –55° C. (It was our impression that the liquid nitrogen technique was much more destructive of vessels than freezing by carbon dioxide ice.) At some subsequent time, varying from 2 to 7 months as we could use the material, each of these bags was innoculated by injecting into it several cubic centimeters of the fluid mixture (Fig. 4) of 8 different organisms which had been also employed for the Group 1 experiments recorded previously. Within 6 to 36 hours, cathode-ray irradiation was given with dosage varying from 1.5 to 6.0 million R. E. P., such exposure requiring but 15 to 60 seconds. The bacterial contamination and the irradiation were carried out while the vascular segments were still frozen. These 43 vessels

were further stored for several weeks in the frozen state, and each was thawed immediately before placing it as a graft into the abdominal aorta of a recipient dog.

Four dogs received aortic segments which had been irradiated with 1.5 million R. E. P. Seventeen dogs received vessels which had been exposed to 2.0 million R. E. P. On these 21 animals the following observations were made. One died on the sixth postoperative day from dehiscence and hemorrhage at both suture lines; *E. coli* was cultured from the graft. Five animals (all of which

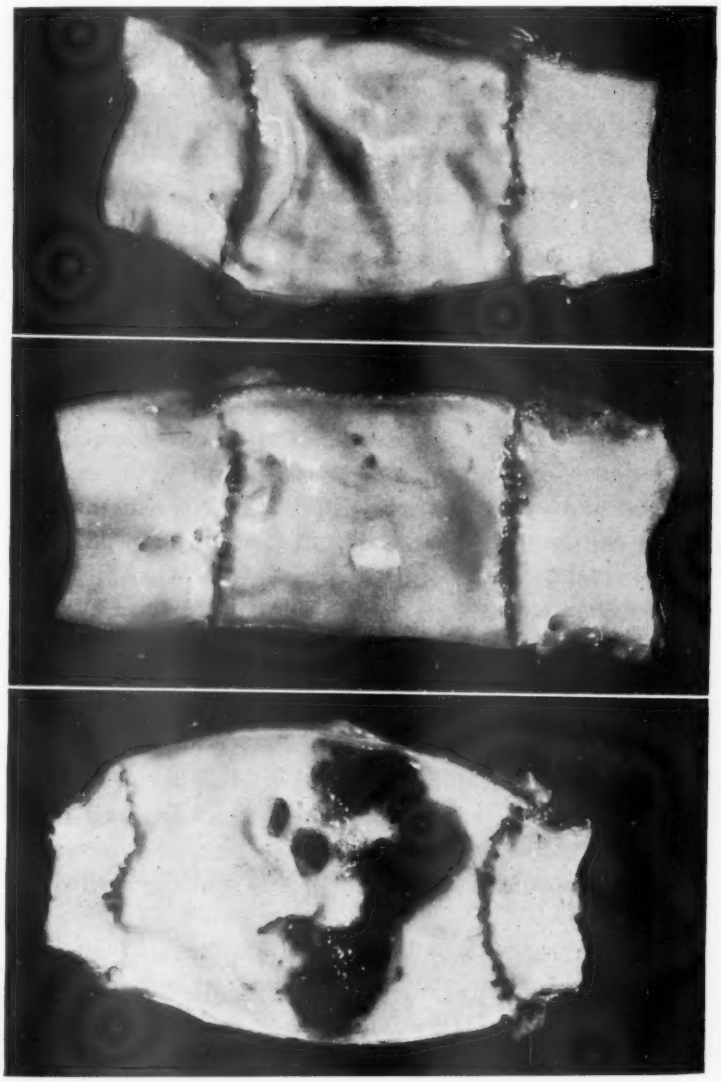

Fig. 5.

Fig. 6.

Fig. 7.

Fig. 5.—Graft from dog sacrificed at 1 year. The graft had been irradiated with 1.5 million R. E. P. (Series 2). It is smooth and in excellent condition.

Fig. 6.—Graft from dog sacrificed at 5 months. The graft had been frozen, heavily contaminated, irradiated with 2.0 million R. E. P. (Series 3). The graft gives an excellent aortic pathway but has several tiny calcified plaques in its wall.

Fig. 7.—Graft from dog sacrificed at 2½ months. The graft had been irradiated with 3 million R.E.P. (Series 3). There are extensive degenerative changes in the vessel wall and large thrombi on its surface.

had grafts with 2 million R. E. P. irradiation) were sacrificed after 2½ months; in each instance there was an excellent aortic pathway, with smooth intima, no mural thrombosis, and no intramural calcification. Two were sacrificed at 5 months; in one of these the graft was in excellent condition except for a tiny mural thrombus 2 mm. in diameter; in the other there were several tiny calcified plaques in the wall (Fig. 6). The remaining 13 dogs are living and have been in good condition for periods of more than 4 months; all have excellent femoral artery pulsations.

Eleven dogs received grafts which had been irradiated with 3.0 miliion R. E. P. Two of these died of distemper less than a month after operation; the excellent appearance of these short-term grafts must be discounted. One animal developed a wound infection and was sacrificed on the fifth postoperative day; *Staph. aureus* was cultured from both the wound and the graft. Six animals were sacrificed after their grafts had been in place for 2 months; 4 of the grafts had mural thrombi 2 to 6 mm. in diameter (Fig. 7) and 1 also showed an area of intimal erosion; 2 of the transplants were in excellent condition. Two animals are living and well, with excellent femoral artery pulsations, more than 2½ months after operation.

Eleven dogs received grafts which had been irradiated with 4.0 to 6.0 million R. E. P. Of these, 3 died on the fifth day of dehiscence at the suture lines, and one developed an occluding thrombus on the tenth day and was sacrificed immediately. Microscopic examination of the 4 specimens revealed no evidence of infection. Two animals were sacrificed at 1 month and 2 later than 3 months; the shorter term grafts appeared to be excellent but the longer term ones showed diffuse intramural calcification in one instance and a very large cylindrical thrombus in the other. Three dogs are still living 4 to 5 months after operation, with apparently normal femoral pulsations thus far.

DISCUSSION

A summary of our observations makes it reasonably clear that cathode-ray irradiation is a potent tool whereby organic material can be sterilized in a very high percentage of cases, but likewise that high dosages of irradiation cause some damage or change in arterial walls which renders them unfit for grafting. Fortunately, it appears that there is an intervening zone of dosage which lies above that necessary to sterilize but which is below that which will damage a vessel wall.

Of the 60 unsterile or intentionally contaminated aortic segments which were irradiated and grafted into recipient animals (Series 2 and 3) only 2 showed evidence of infection. It would appear that irradiation by at least 1.5 million R. E. P. is necessary to secure sterility with a high degree of regularity. This dose has produced sterility in more than 95 per cent of vessels which were known to be heavily contaminated with bacteria; a higher percentage might possibly be attained if more massive doses were employed.

As far as damage to vessel walls is concerned—as judged by gross appearances of the irradiated grafts some months after their implantation into

recipient animals—dosages of irradiation at 1.5 million were seldom followed by serious changes in the graft wall, whereas doses at 3.0 million R. E. P., or above, produced severe and irreparable changes in many of the tests.

The borderlines of optimum irradiation dosage are not sharply defined, but the studies thus far would seem to indicate that the range between 2.0 million and about 2.5 million R. E. P. gives the best results; in this zone sterilization is nearly always achieved and tissue damage is minimal or absent. It must be emphasized that these statements hold only when irradiating tissues which are frozen; irradiation of tissues at room temperatures produces drastic alterations in enzyme systems and organic composition. We have been extremely encouraged by the results obtained when using infected frozen aortic segments which were treated by cathode-ray irradiation (between 2.0 and 2.5 million R. E. P.) before employing them as aortic grafts in recipient dogs; the early appearances of these aortic pathways compare favorably with those obtained previously in our laboratory using a fluid-medium technique of preservation of sterile blood vessels.[3]

It hardly needs to be added that homologous grafting of blood vessels will always be best accomplished by acquiring sterile vascular segments and storing these in a frozen state, or preferably, preserving them in fluid media[3] until such time as they are needed for grafting. While this is the ideal and can often be accomplished, it is sometimes difficult to obtain from human bodies appropriate vascular segments which are sterile. We must, therefore, seek methods which can conceivably sterilize vessel segments which are acceptable in every way except for the fact that they may be infected. A large amount of such material is available from post-mortem subjects within a few hours after death. Of the various methods we have studied to date for sterilization of such infected material, the cathode-ray irradiation is the only one which has given acceptable results when the treated vessels have been used for grafts. While this method seems to be reasonably safe and effective, it has an obvious disadvantage in that the apparatus which is required is available in only a few communities. Aside from this one objectionable feature, our preliminary studies indicate that high voltage cathode-ray irradiation of frozen arterial segments provides a quick and effective method of sterilizing and storing blood vessels which can be subsequently used as vascular grafts. To date we have employed this method of grafting for two human beings with coarctation of the aorta in whom it was necessary to bridge long aortic gaps which could not be overcome by primary anastomosis. These patients have been followed only 2 and 6 months, respectively, since operation; there has been complete relief of hypertension in each.

SUMMARY

A method is presented for the sterilization of contaminated vascular segments by irradiating them with high-voltage cathode rays. Description is given of the results obtained by implanting 60 nonsterile or purposely infected aortic segments which were irradiated prior to their use as aortic grafts in recipient dogs. Various dosages of irradiation are discussed in relation to their effec-

tiveness in sterilization and to their harmful action on the vessel walls. Irradiation between 2.0 million and 2.5 million R. E. P. appears to give satisfactory sterilization and inflicts very little tissue damage.

REFERENCES

1. Brasch, A., Huber, W., Friedemann, U., and Traub, F. B.: Action of High Intensity Electrons on Biological Objects, Proc. Rudolf Virchow Medical Society, New York, **8**: 1, 1949.
2. Dunn, C. G., Campbell, W. L., Fram, H., and Hutchins, A.: Biological and Photo-Chemical Effects of High Energy, Electrostatically Produced Roentgen Rays and Cathode Rays, J. Appl. Phys. **19**: 605-616, 1948.
3. Gross, R. E., Bill, A. H., Jr., and Peirce, E. C., II: Methods for Preservation and Transplantation of Arterial Grafts, Surg., Gynec. & Obst. **88**: 689-701, 1949.
4. Lea, D. E.: Actions of Radiations on Living Cells, New York, 1947, The Macmillan Company, Cambridge University Press.
5. Peirce, E. C., II, Rheinlander, H. F., Moritz, A. R., Gross, R. E., and Merrill, K., Jr.: Transplantation of Aortic Segments Fixed in Four Percent Neutral Formalin, Am J. Surg. **78**: 314-323, 1949.
6. Segnitz, R., and Gross, R. E.: Unpublished data.
7. Trump, J. G., and Van de Graaff, R. J.: Irradiation of Biological Materials by High Energy Roentgen Rays and Cathode Rays, J. Appl. Phys. **19**: 599-604, 1948.
8. Trump, J. G., and Van de Graaff, R. J.: A Compact Pressure-Insulated Electrostatic X-Ray Generator, Physiol. Rev. **55**: 1160-1165, 1939.

THE SURGICAL TREATMENT OF CARDIAC VALVULAR STENOSIS

WILLIAM H. MULLER, JR., M.D., AND W. P. LONGMIRE, JR., M.D.,
LOS ANGELES, CALIF.

(From the Department of Surgery, School of Medicine, University of California at Los Angeles)

DURING the past several years considerable progress has been achieved in the surgical treatment of stenosis of the cardiac valves by direct attack upon these deformities. This progress has been stimulated by the major advances made in the development of surgical procedures for the treatment of congenital cardiovascular defects such as patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, and others.

Efforts to deal directly with the stenotic mitral valve have been more vigorous than corresponding efforts to treat the stenotic pulmonic valve. In 1913, Doyen[1] attempted unsuccessfully to divide a structure which was thought to be pulmonic valvular stenosis but which at post-mortem examination proved to be infundibular stenosis. Attempts to perform pulmonic valvulotomy were not reported again until 1948, when Brock[2] successfully divided 3 such valves. About the same time Sellors[3] described one case of pure pulmonic stenosis in which he had successfully performed a valvulotomy. In April, 1950, Blalock and Kieffer[4] recorded the results of treatment of 19 patients by the Brock method, and in September, 1950, Potts and associates[5] reported that they had performed 4 operations with the aid of a valvulotome that they had designed and made from a tenotomy knife. The procedure in these operations was similar to the Brock method. All but 2 of Blalock and Kieffer's patients survived the procedure. One of these had a chronic brain abscess which had not been suspected. The other had had an artificial ductus created previously to correct an anomaly diagnosed as the tetralogy of Fallot. Brock and Campbell[6] subsequently reported the results of valvulotomy in 33 cases of pulmonic stenosis, 18 of which were diagnosed as pure pulmonic stenosis.

After the initial attempts of Cutler and Levine,[7] Allen and Graham,[8] and others, little progress was made in the development of a procedure for the relief of mitral stenosis either in patients or in laboratory animals until immediately after World War II. At this time Smithy,[9, 10] Harken and colleagues,[11] and Bailey and co-workers[12-15] devoted considerable effort to the problem. Smithy carried out essentially the procedure which Cutler used, a method which was based upon the supposition that a regurgitant lesion is much better tolerated than a stenotic one. Harken[11] devised a procedure, which he called valvuloplasty, in which a portion of the valvular ring in the region of the commissures is excised. Bailey originated an operation which he termed commissurotomy. This consists of incising the valve ring through

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the commissures. To facilitate the technique, he devised a method by which the index finger with a small valvulotome concealed beneath the second glove is introduced through the auricular appendage. With the instrument in this position, the commissures may be identified and incised. In his most recent report,[16] 86 patients had been operated upon, 12 of whom died. Of the last 60 patients, however, only 4 died.

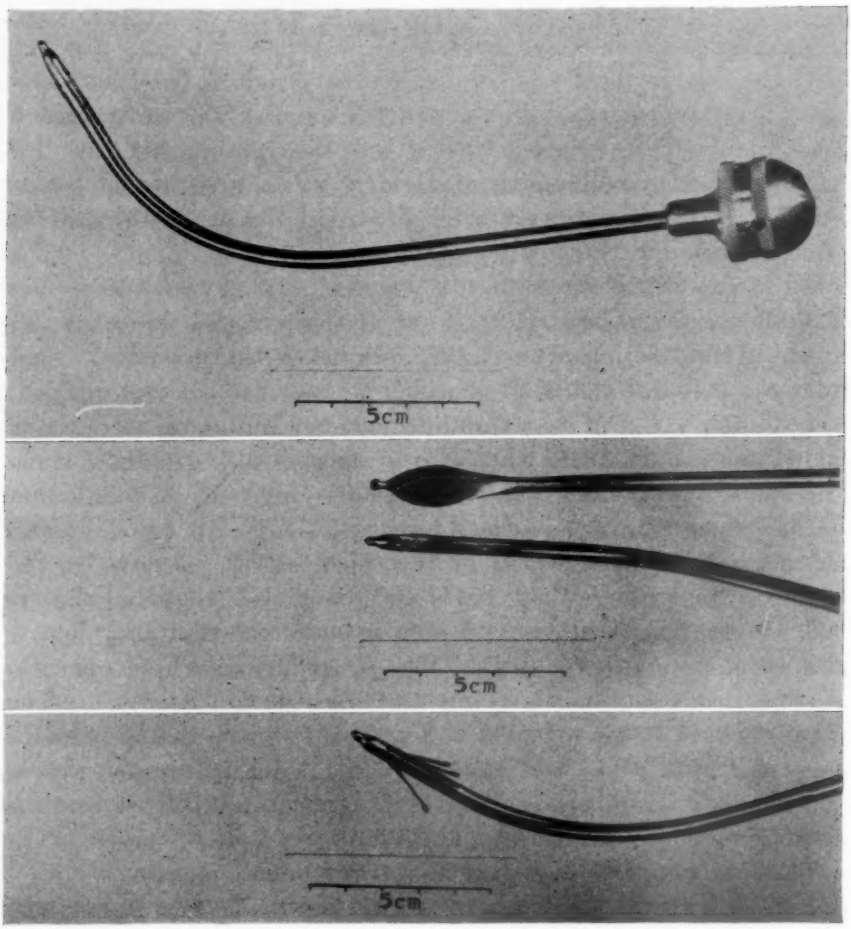

Fig. 1.—Adjustable valvulotome for incising stenotic pulmonic valve. *A*, Over-all view of pulmonic valvulotome; *B*, closed leading end of valvulotome compared to Brock valvulotome; *C*, open leading end of valvulotome showing 3 blades. Blades are sharp on leading edge but blunt on end.

This presentation is a report of valvulotomy performed on 5 patients with pure pulmonic stenosis and of commissurotomy performed on 14 patients with mitral stenosis. All the patients with pure pulmonic stenosis and 8 of those with mitral stenosis had diagnostic studies including cardiac catheterization.*

PURE PULMONIC STENOSIS

Pure pulmonic stenosis, as the name implies, signifies stenosis of the pulmonic valve without an associated abnormality. The name is inaptly used when

*Performed by Dr. George C. Griffith, Dr. Richard Cosby, Dr. David Levinson, and Dr. Willard Zinn at the Cardiac Clinic of the Los Angeles County General Hospital.

thus applied, however, because the majority of patients with pulmonic stenosis have an auricular septal defect. They differ from patients with the tetralogy of Fallot chiefly in that they have an intact ventricular septum. Cyanosis is absent in patients who do not have a patent foramen ovale but may be intense in those who do have one, the intensity depending upon the size of the right-to-left shunt and upon the degree of stenosis. Although upon first consideration one

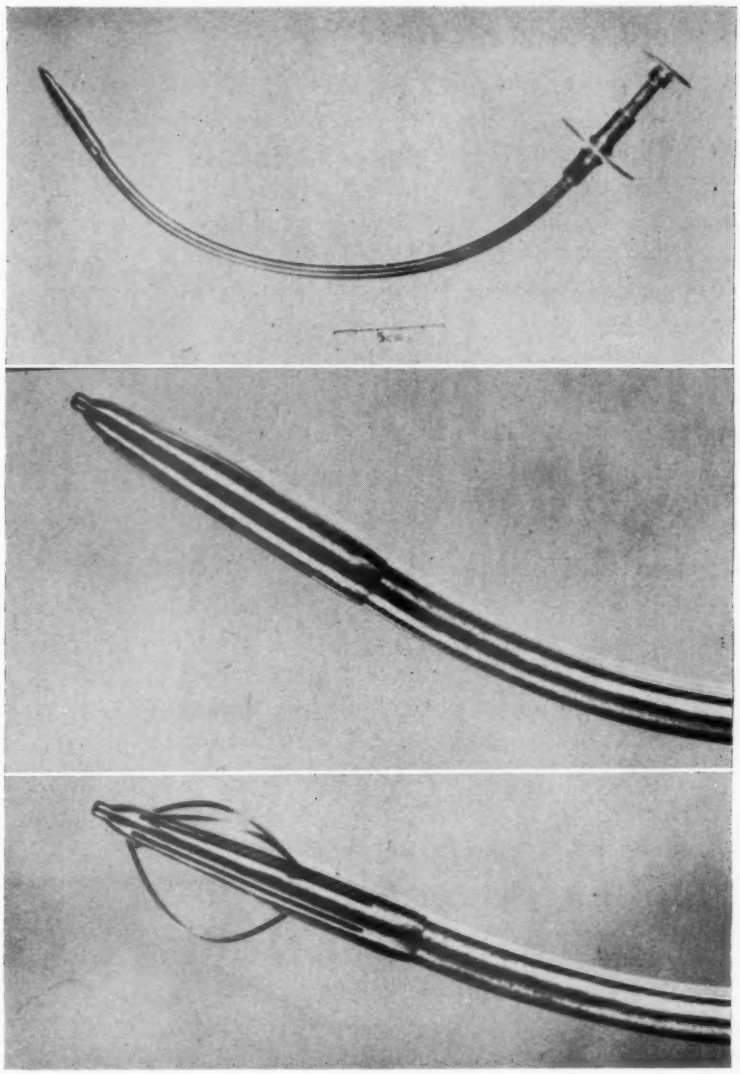

Fig. 2.—Instrument used for dilating the incised pulmonic valve. *A*, Over-all view of pulmonic valve dilator; *B*, end of dilator closed; *C*, end of dilator open.

would expect a systemic pulmonary anastomosis to benefit these patients, Blalock and Kieffer[4] pointed out that this procedure increases the pulmonary venous return to the left auricle, thus diminishing the flow of blood through the patent foramen ovale, which has served as an overflow valve for the right side of the heart.. This change in blood flow has produced right-sided heart failure in patients with pure pulmonic stenosis who have been treated by this procedure.

Pure pulmonic stenosis may be of 2 types. In one the valve itself becomes stenotic and in the other the infundibulum or the region of the pulmonary conus just beneath the valve may hypertrophy excessively, producing stenosis. Fortunately, the valvular type occurs more frequently and is the one which can be alleviated by valvulotomy.

Operative Technique.—We have operated upon 5 patients with pure pulmonic stenosis. In each case we have adhered to the principles of the method developed by Brock.[2, 6] We followed his procedure exactly in our first operation. We felt, however, that his valvulotome presented certain slight disadvantages. As Potts has pointed out, the defect made in the wall of the ventricle by the Brock valvulotome is as large as the blade of that instrument. The pulmonary artery sound presents the same disadvantage. As a pulmonary artery sound was unobtainable, we used a large, curved hemostat. Spreading the hemostat increased the size of the incision in the ventricle, resulting in considerable blood loss. We felt that an instrument of small diameter which might be expanded after it was passed through the ventricular wall might obviate these disadvantages. We thus devised an instrument with several spring steel dilating elements which are pivoted at either end and which curve convexly when pressure is applied through a flexible shaft[17] (Fig. 2). We felt that this instrument might tear the lines of fusion of the valve leaflets, but we have been unable to prove this. We employed this instrument on the second patient and expanded the valve to the size of the main pulmonary artery. We abandoned an attempt to use it on the third patient because the heart was too small to accommodate the instrument.

Since we did not know what changes the expansible valvulotome produced in the pulmonic valve, we wondered about the ultimate fate of a valve treated in this manner. It would seem that, if only dilatation were accomplished, stenosis might recur. In order to prevent this possibility we devised a similar instrument with 3 small blades which might be opened into the cutting position after they had been passed into the right ventricle (Fig. 1). With it we use the expansible dilator to dilate the incised valve (Fig. 2). We have satisfactorily treated the last 2 patients in this manner.

The operative procedure which we employ at the present time is as follows: The patient is given penicillin, 300,000 units every 6 hours, and a proper dosage of quinidine for 2 days prior to operation. Pre-anesthesia medication of scopolamine and morphine sulfate is given. An anesthetic, usually cyclopropane, oxygen, and ether, is administered. The patient is placed in the supine position on the operating table with the left shoulder slightly elevated and with the left arm flexed at the elbow so that the axilla is accessible. An anterolateral incision is started at the sternum and extended well into the axilla over the course of the fourth intercostal space. At times the costal cartilage of the fourth rib must be divided in order to facilitate exposure. About 10 c.c. of 4 per cent Novocain is then injected into the pericardial cavity and allowed to remain for about 5 minutes before the pericardium is entered. The pericardium is then incised longitudinally about 1 cm.

anterior to the phrenic nerve and held open with stay sutures. Novocain is injected into the right ventricular wall about 2 or 3 cm. from the origin of the pulmonary artery, and two stay sutures are placed in the ventricular muscle.

Fig. 3.

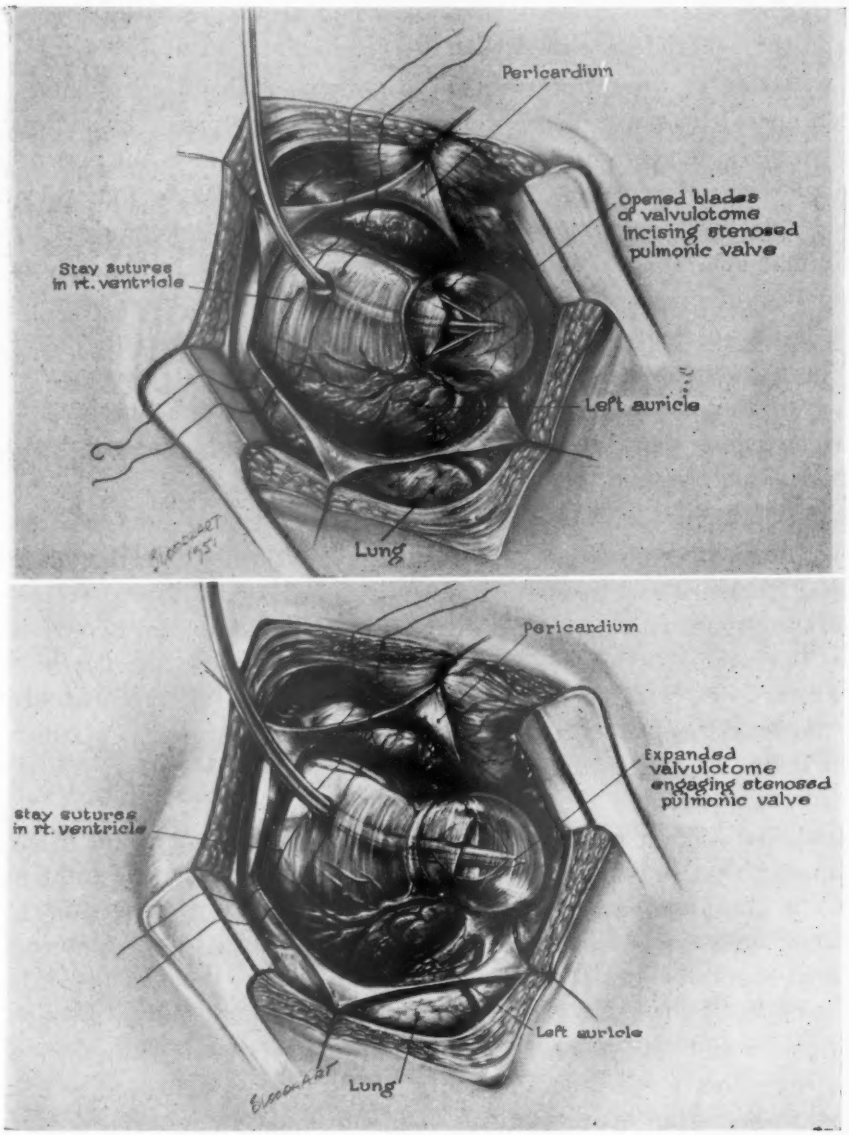

Fig. 4.

Fig. 3.—Drawing of operative exposure for pulmonic valvulotomy showing valvulotome introduced through stab wound in right ventricle and open blades incising stenosed pulmonic valve.

Fig. 4.—Drawing of operative exposure for pulmonic valvulotomy showing expansible dilator introduced through stab wound in right ventricle and engaging and dilating incised pulmonic value.

With a sharp-pointed knife an incision is made through the full-thickness of the ventricular wall. Bleeding is controlled with the finger. The valvulotome is then slipped into this opening, and the stenosed orifice is usually located

with ease. The blades are opened slightly to a cutting position, and the leading end of the instrument is pushed through the stenotic valve. The end of the instrument is withdrawn into the ventricle, the blades are opened wider, and the valve is again incised (Fig. 3). The expansible dilator is then inserted, and the incised valve is dilated (Fig. 4). The dilator is withdrawn, and the incision in the ventricle is closed with interrupted silk sutures.

Presentation of Case Material.—Five patients with pure pulmonic stenosis have been operated upon. There were 4 females and 1 male. The oldest was 30 and the youngest 4 years of age. Cyanosis was absent in 3 but was present in 2. The exercise tolerance of 2 was markedly diminished so that they became extremely fatigued on walking less than a block. The 30-year-old patient had only minimal symptoms. At the age of 15 years she noticed occasional very mild shortness of breath upon exertion. She was told that she had a loud heart murmur, but no diagnosis was made at that time. The symptoms did not change until 5 or 6 months prior to admission, when she began to have slightly increased dyspnea upon exertion. Catheterization revealed a marked differential between the right ventricle and the pulmonary artery. It was thus decided that a valvulotomy should be performed on this patient.

All these patients improved after valvulotomy. One patient was recatheterized 3 months after operation and, although a definite lowering of the right ventricular pressure was present, it was still appreciably above normal. In all these patients there was marked poststenotic dilatation of the main pulmonary artery at operation. A marked thrill was present in every instance in the main pulmonary artery. This persisted after valvulotomy but became less intense. A systolic murmur was present over the pulmonic area in all patients before operation and persisted after valvulotomy. It was, however, less harsh and intense than before operation.

Discussion.—From the increasing number of reports in the literature it would appear that valvulotomy is a satisfactory treatment for pure pulmonic stenosis. A considerable period of time must elapse before one can be sure of the ultimate outcome of this procedure. Such factors as the permanence of the incisions in the valve and the effect of slight pulmonic insufficiency, which may be produced upon the right ventricular muscle, will determine its value.

We performed valvulotomy with the aid of the Brock valvulotome upon the first patient whom we treated surgically. This patient improved greatly in the first few weeks after operation and has continued to improve. However, a thrill in the pulmonic area, which was present before operation and which was absent for 2 to 3 months after operation, has since returned. It is less intense than previously, however. This might indicate that the incision in the valve has become smaller than it was when it was made. The recurrence of the thrill and the continued elevation of the right ventricular pressure after operation are some of the factors which prompted us to devise the 3 bladed instrument. One would assume that the degree of pulmonic insufficiency produced would not be a serious problem. It seems logical that a right ventricle which is accustomed to

a systolic pressure often higher than 100 mm. Hg in these patients would tolerate without difficulty a moderate degree of insufficiency if it is produced. A considerable period of time must elapse before one can be sure of the ultimate benefit that this procedure offers. Such factors as the permanence of the incisions will determine this. Immediate endothelization of the incised surfaces would be the most desirable result. As there are no satisfactory laboratory methods of producing pulmonic stenosis which simulates the scarred and thickened valve of congenital pulmonic stenosis, it will be necessary to examine pulmonic valves in patients who have been subjected to valvulotomy and who have died some years after operation. Recently, in the laboratory, we have been able to divide the pulmonic valves in dogs under direct vision by shunting the blood temporarily around the main pulmonary artery. We believe that this method or some modification might be applied to patients.

Patients have tolerated the procedure well and have improved after operation in most instances. The procedure presents no difficult technical problems, and the mortality rate is progressively decreasing. Because of these considerations it would seem advisable to perform the operation on patients in whom the diagnosis of pure pulmonic stenosis is made.

MITRAL STENOSIS

The development of a satisfactory method for the surgical treatment of mitral stenosis is an important advance in cardiovascular surgery because it paves the way for the surgical treatment of other acquired cardiac deformities. The idea of incising the mitral valve surgically was first suggested in 1902 by Sir Laughton Bunton, an English physician, after he had examined a markedly stenotic and calcified mitral valve in a patient who had died of rheumatic heart disease. The majority of patients with mitral stenosis live almost normal lives, some with only slightly limited activity. Approximately 5 to 10 per cent of the patients with this defect, however, do have progressive symptoms of pulmonary hypertension with its manifestations, which may rapidly result in death.

The diagnosis of mitral stenosis in patients with advanced lesions usually presents no difficulty. Very early lesions might present some problem, however. It is helpful to obtain a history of rheumatic fever. This history can be obtained in as high as 70 per cent of patients with rheumatic heart disease, and in another 5 to 10 per cent a history of chorea without rheumatism may be elicited. In the presence of early lesions there may be little or no enlargement of the heart and only a soft diastolic murmur at the apex and along the left border of the sternum, transmitted into the axilla. However, when there has been long-standing obstruction of the mitral orifice, the heart is usually enlarged, and not only a diastolic, but, in most instances, a systolic murmur can be heard.

Until recent years all attempts to relieve mitral stenosis by direct attack upon the mitral valve employed a procedure which, in relieving the stenosis, produced mitral regurgitation. Bailey and Harken were among the first to emphasize that a procedure designed for this purpose should relieve the stenosis

but at the same time produce a minimal amount of regurgitation or none at all. Although most previous approaches to the mitral valve have been through the left ventricle, both Bailey and Harken approached the valve through the left auricle. Harken designed an instrument with which he excised a portion of the valve commissure after passing the instrument first through the left superior pulmonary vein, but later through the auricular appendage. Bailey[12] developed a method whereby he inserted his finger, along which lay a small, hooked valvulotome concealed beneath a second glove, through the left auricular appendage. By this maneuver he was able to palpate the valve and incise the areas of the commissures. He subsequently devised a ratchet knife with a shearing action which divides the calcified ring more easily. By lengthening the slit at either end, some valve function of the leaflets is maintained, and theoretically at the same time little or no regurgitation is produced. Brock has employed a similar method but has attempted to tear the commissures with the finger rather than with a cutting instrument. He reported satisfactory results with this method.

Operative Technique.—In our first patient we used the Bailey hooked knife and had difficulty dividing the extremely calcified commissure with this instrument. We also had difficulty pronating the hand sufficiently to divide the posteromedial commissure. We therefore devised an instrument similar to Bailey's ratchet knife with some slight modifications (Fig. 5). Our instrument has a hook on either side rather than on only one. Furthermore, it is curved transversely to fit the transverse curvature of the finger. Because of this curvature we have found it unnecessary to wear a second glove; we feel that this allows much greater maneuverability and permits the commissures to be engaged in the instrument with greater facility. The instrument has 2 blades so that a shearing action is obtained.

The procedure which we use is as follows: The patient is given penicillin, 100,000 units every 6 hours, 3 days prior to operation, and is given quinidine up to doses of about 6 gr. every 4 hours during the same period. Pre-anesthesia medication consists of scopolamine and morphine. Anesthesia, usually Sodium Pentothal and endotracheal ether, is administered. The patient is placed in the supine position on the operating table and the left shoulder is slightly elevated. The chest is entered through an anterolateral incision in the fourth intercostal space. If necessary the fourth costal cartilage is divided at its junction with the sternum. We previously used the third intercostal space but found that this made the exposure too high for proper access to the left auricle. About 10 c.c. of 4 per cent Novocain is instilled into the pericardial cavity and allowed to remain for 4 to 5 minutes before the pericardium is opened. A long, curved incision is then made in the pericardium in such a manner that a flap is formed, the base of which is anterior and parallel to the phrenic nerve. A purse-string suture of No. 00 silk on an atraumatic needle is placed about the auricular appendage at its junction with the chamber of the auricle. The auricle is temporarily occluded by a special nonerushing clamp and the tip of the appendage is excised. The finger is then introduced into the auricle and the valve

is palpated. In most instances a jet of blood can be felt passing into the auricle through the stenotic orifice with each systole. Calcification of the valve is usually present. The finger is passed into the valve opening, which is then moderately dilated. If it is noted that one of the commissures tears easily, an attempt is made to continue this tear. The posteromedial commissure tears most easily, but in most instances we have been unable to tear either. At this point the valvulotome is passed into the auricle along the finger, and the anterolateral commissure is usually engaged first and divided (Figs. 6 and 7). The

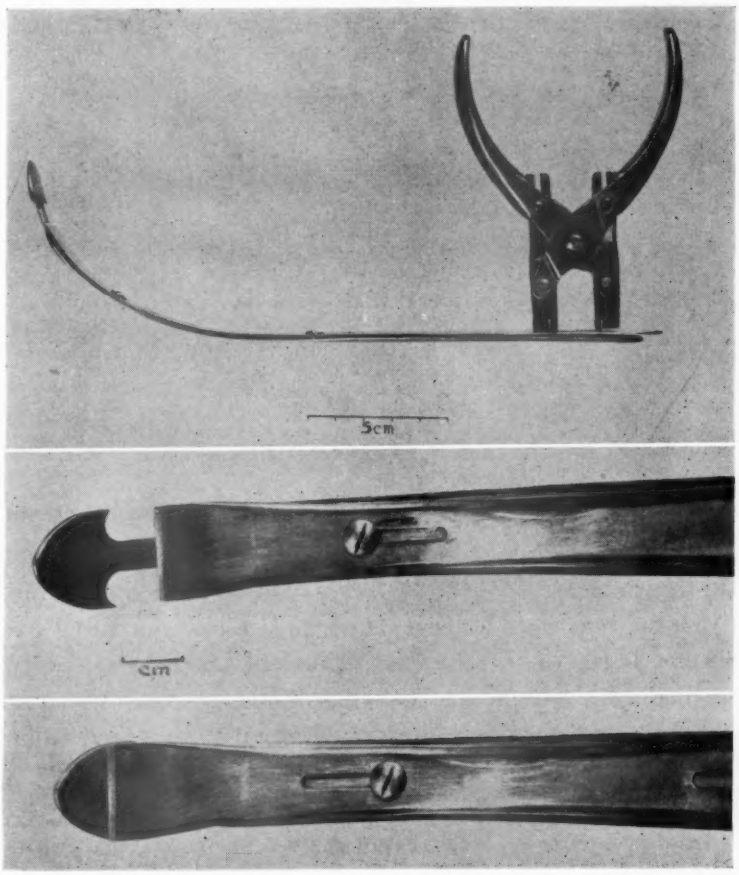

Fig. 5.—Photograph of valvulotome used for mitral commissurotomy. *A*, Over-all view of valvulotome; *B*, open end of valvulotome showing hooked knife on both sides; *C*, end of valvulotome with shearing blade closed.

valvulotome is then moved to the right and the posteromedial commissure is engaged and also divided. The incised areas are then slightly dilated. The finger is withdrawn, the purse-string suture is tightened, and the cut end of the auricle is oversewn with an arterial suture. The pericardium is closed loosely, the chest is closed in the usual manner, and intrapleural catheter drainage is instituted.

Presentation of Case Material.—We have operated on 14 patients. The oldest in our series was 51 and the youngest 22 years of age. Eight were over 35. Six were females and 8 were males. A history of rheumatic fever was

obtained from all but 2 of our patients. A history of symptoms of rheumatic heart disease which lasted from 6 months to 20 years was elicited. Nine had advanced pulmonary hypertension with pulmonary edema and hemoptysis. Six had peripheral emboli which resulted in residual hemiplegia in 2. Five patients had had auricular fibrillation before operation. Two had reverted to normal rhythm after the administration of quinidine prior to the operative procedure.

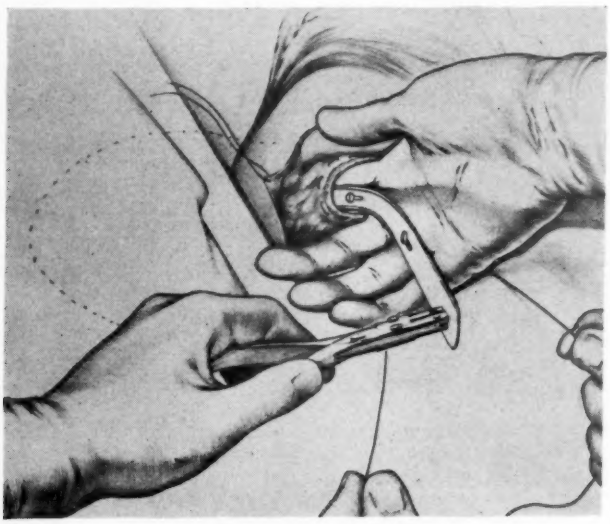

Fig. 6.—Drawing showing right index finger and mitral valvulotome introduced into left auricle through left auricular appendage.

In the first patient only the anterolateral commissure was divided; in all the others both commissures were incised. Calcification of the valve was present in all our patients. Three of the patients whom we treated surgically died. The first of these died of a pulmonary embolus 3 weeks following operation. The cause of death was confirmed at autopsy. The valve appeared to be adequately divided. She was ambulatory until immediately before death and was ready to be discharged from the hospital. She appeared to be much improved before the pulmonary embolus occurred. The second patient whom we treated surgically was a 42-year-old man with long-standing rheumatic heart disease manifested by both aortic and mitral lesions. We performed a valvulotomy on this patient. After we removed the valvulotome from the auricle, we noted a tear in the auricular wall. A moderate amount of bleeding ensued before we could close the tear. Cardiac arrest occurred and contractions could not be re-initiated. The eleventh patient in our series also died. This patient was a 38-year-old man with long-standing rheumatic heart disease. He was in constant heart failure and had liver congestion to the point of having jaundice. He also had infiltrating lesions in both lung fields, the cause of which was not known. Because he was in constant heart failure and because there was nothing else to offer this patient, we treated him by valvulotomy. He withstood the pro-

cedure without mishap. However, on the third postoperative day, auricular fibrillation began and was accompanied by a very high pulse deficit; cardiac dilatation and failure ensued despite all therapy. He died on the fourth postoperative day.

One of the surviving patients had the clinical signs and symptoms of an embolus to the left kidney although laboratory findings did not confirm it. Another was thought to have a small pulmonary embolus, but again this could not be confirmed. We feel that all the surviving patients have improved subjectively. In the oldest patient operated upon, a diastolic murmur persists.

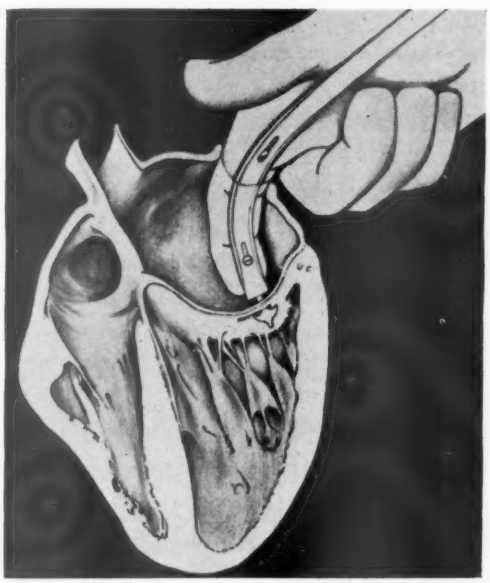

Fig. 7.—Cut-away drawing of heart with right index finger and mitral valvulotome introduced into left auricle. The anterolateral commissure is engaged in one side of the open valvulotome. The valvulotome is then moved to the other side to engage the posteromedial commissure.

It is too early to evaluate the result of his operation, but he appears to be improved. Systolic murmurs have been present in 8 of these patients after operation. However, other than in the one mentioned, a diastolic murmur has been absent. All our patients have been maintained on proper doses of digitalis and quinidine after operation. Auricular fibrillation begins in many of these patients on the third to the sixth postoperative day, and a larger amount of quinidine than before operation may be necessary to prevent this or to produce a normal rhythm.

DISCUSSION

In selecting candidates for commissurotomy one should consider that young patients are best suited to undergo the operation. We feel that the duration of symptoms of rheumatic heart disease is equally important. As Bailey has emphasized, the most suitable candidates are young patients with only increasing exertional dyspnea and easy fatigability rather than those with symptoms of advanced pulmonary hypertension. The prognosis is prob-

ably poorer in patients with auricular fibrillation and a history of emboli, pulmonary edema, and hemoptysis. We believe that only aortic insufficiency severe enough to produce peripheral signs should contraindicate operation. We have operated upon 3 patients who were thought to have mild to moderate aortic insufficiency. Two appeared to benefit considerably from the operation. Other obvious contraindications are acute rheumatic fever, subacute bacterial endocarditis, and recent emboli.

We have been unable to establish definite criteria for the selection of our patients. We wish to recommend, however, that the boundaries of operability be extended to include a greater number of patients with advanced mitral stenosis. While younger patients tolerate and respond to commissurotomy much better than older patients, more of the latter group should be given the opportunity to have operative relief of the stenosis. Also, patients with far-advanced signs and symptoms of pulmonary hypertension who might be considered borderline candidates for operation should be included. We do not wish to imply that the greatest efforts should be concentrated upon this group of patients. We agree with Bailey that young people with minimal symptoms of relatively short duration have the most favorable prognosis.

A correlation of preoperative and postoperative catheterization findings with clinical signs and symptoms should prove to be of value in the selection of patients for operation. Insufficient time has elapsed for postoperative catheterization in all our patients.

As in pulmonic stenosis, the high incidence of improvement after operation, the facility with which the procedure can be accomplished, and the progressively decreasing mortality rate in patients with mitral stenosis upon whom commissurotomy is performed should promote its use in more patients with this deformity.

SUMMARY

Experiences in the treatment of pure pulmonic stenosis and mitral stenosis by valvulotomy are presented.

Five patients with pure pulmonic stenosis were successfully operated upon by a procedure which incorporated the principles of the Brock method. An adjustable valvulotome with 3 cutting blades was used satisfactorily in the last 2 patients; dilatation of the incised valve was accomplished with an expansible dilating instrument.

Fourteen patients were operated upon for mitral stenosis by Bailey's technique of commissurotomy. Eleven of these patients survived.

A valvulotome which is a modification of Bailey's is described. It has a hooked knife on either side and is designed to obviate the necessity for a second glove.

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REFERENCES

1. Doyen, E.: Cited by Dumont, J.: Chirurgie des malformations congenitales ou acquises du coeur, Presse med. **21**: 860, 1913.

2. Brock, R. C.: Pulmonary Valvulotomy for Relief of Congenital Pulmonary Stenosis, Brit. Med. J. 1: 1121, 1948.
3. Sellors, T. H.: Surgery of Pulmonary Stenosis, The Lancet 1: 988, 1948 (New Series).
4. Blalock, Alfred, and Kieffer, Richard F., Jr.: Valvulotomy for the Relief of Congenital Valvular Pulmonic Stenosis With Intact Ventricular Septum; Report of 19 Operations by the Brock Method, Ann. Surg. 132: 496, 1950.
5. Potts, Willis J., Gibson, Stanley, Riker, William L., and Leininger, C. R.: Congenital Pulmonary Stenosis With Intact Ventricular Septum, J. A. M. A. 144: 8, 1950.
6. Brock, R. C., and Campbell, Maurice: Valvulotomy for Pulmonary Valvular Stenosis, Brit. Heart J. 12: 377, 1950.
7. Cutler, E. C., and Levine, S. A.: Cardiotomy and Valvulotomy for Mitral Stenosis, Boston M. & S. J. 188: 1023, 1923.
8. Allen, D. S., and Graham, E. A.: Intracardiac Surgery, a New Method, J. A. M. A. 79: 1028, 1922.
9. Smithy, H. G., and Parker, E. F.: Experimental Aortic Valvulotomy; A Preliminary Report, Surg., Gynec. & Obst. 84: 625, 1947.
10. Smithy, H. G.: An Approach to the Surgical Treatment of Chronic Valvular Disease of the Heart, Presented at the sixteenth annual assembly of the Southeast Surgical Congress, Hollywood, Fla., April 5-8, 1948.
11. Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis, New England J. Med. 239: 801, 1948.
12. Bailey, C. P.: The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy), Dis. of Chest 15: 377, 1949.
13. Bailey, C. P., Glover, R. P., and O'Neill, T. J. E.: The Surgery of Mitral Stenosis, J. Thoracic Surg. 19: 16, 1950.
14. Glover, R. P., O'Neill, T. J. E., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, Circulation 1: 329, 1950.
15. O'Neill, T. J. E., Glover, R. P., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, J. Internat. Coll. Surgeons 13: 355, 1950.
16. Glover, R. P., Bailey, C. P., and O'Neill, T. J. E.: Surgery of Stenotic Valvular Disease of the Heart, J. A. M. A. 144: 1049, 1950.
17. Muller, W. H., Jr., and Longmire, W. P., Jr.: The Surgical Treatment of Pure Pulmonic Stenosis; A Description of an Expansible Valvulotome, to be published in SURGERY.
18. Taussig, Helen B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.

DISCUSSION

DR. RICHARD VARCO.—These days an individual arising to discuss a phase of the surgical treatment of heart disease who is unable to introduce a new instrument feels almost conspicuous. Lest we be justly accused of harboring stunted imaginations at the University of Minnesota, we wish to suggest a type of procedure that is somewhat different from techniques in standard usage for correcting valvular pulmonic stenosis. The development of this approach stems from 2 considerations.

First, there is an appreciation of the surgical principle that operative techniques carried through under direct vision are usually superior to those in which maneuvering is blindly done.

Second, we sought to improve the condition in some patients with tetralogy of Fallot so as to convert a cardiac situation harboring 5 defects, as exists after standard treatment, to an anomalous heart with but 2 or 3 defects. It is conceded that lessening the number of shunts might not improve the eventual prognosis. It would surely be closer to an eventual total correction of this deformed heart however. Therefore, as a regular part of the exploration in tetralogy cases, we have come to open the pericardium widely and palpate the region of the origin of the pulmonary artery, feeling for a valvular type of stenosis. It was surprising to us to learn that about 30 per cent of the cases possessed a valvular type of stenosis. This has been largely corroborated by an independent study by pathologists elsewhere who examined nearly 100 tetrads and found about 25 per cent carried a stenotic valvular component. If it were possible in this group to remove the valvular component, theoretically one would have reduced rather than increased the cardiac disability. Potentially, and for the future, one could hope to return and correct the ventricular septal defect. With this motivation, we have sampled in the laboratory the tolerance of the heart for cross clamping the aorta, the pulmonary artery, or the caval inflow. We propose to explore the tolerance of the heart to cutting off the entire cardiac filling, both from the

lungs as well as from the systemic circuit. We can say, however, at the present time that the dog tolerates very poorly cross clamping of the aorta and tolerates but slightly better cross clamping of the pulmonary artery. He tolerates reasonably well cross clamping of both the superior and inferior venae cavae; the former, cardiac to the azygos vein, and the latter, inferior to the hepatic vein, can be occluded for periods up to 4 minutes with eventual recovery. With these cross occluded, it is possible to work in a field relatively dry save for the coronary venous return.

(Slide 1.) With the venae cavae cross clamped, an interval of 6 to 12 heartbeats is allowed to elapse so that the heart becomes flaccid and continues to squirm. The pulmonary artery, which has been dissected free from the aorta down to the origin of its two segments, the right or left pulmonary arteries, is now cross clamped and a transverse or longitudinal incision is made in the pulmonary artery. The cervixlike pulmonary valvular stenosis is grasped and incised under direct vision with the scissors. It has usually been relatively easy to convert this to a bicuspid type of valve. Allis forceps, or a Potts type ductus clamp, are used to approximate the free edges of the pulmonary arterial rent. The clamps are removed from the distal pulmonary artery, secondarily the venae cavae. At one's leisure, the defect in the pulmonary trunk is sutured, without cardiac or vascular embarrassment, since a stream flows even more freely than before due to relief from the valvular stenosis.

(Slide 2.) Data is presented here from pre- and postoperative cardiac catheterization studies in a child with pure pulmonary stenosis. You can note a preoperative right ventricular pressure of 260/0 and a cardiac output of 1 L. per minute. Following surgery the right ventricular pressure dropped to 60/0, and the cardiac output rose to 2.1 L. per minute. In the first 5 individuals operated upon, there have been 4 clinical successes. One individual died just as the chest was being opened preparatory to the dissection of the great vessels. We have since operated upon a sixth individual and in this case with the venae cavae occluded, whereas the heart emptied satisfactorily, as soon as the pulmonary artery was cross clamped the right ventricle filled under great tension, indicating an internal shunt that had not heretofore been recognized. The clamps were then removed and the standard procedure as developed by Brock was safely carried out in this individual. Surgeons may well be reasonably reluctant to spend the additional time required for dissecting out the inflow-outflow vessels to the heart, particularly in a patient with a heart at times intolerant of such manipulations. This drawback is recognized, and is indicated in the preface to the technical description.

Any merits found in the procedure, by virtue of the direct visual approach and the plan for correcting rather than palliating, must balance out such objections, therefore, if it is to fill any useful purpose.

DR. WILLIAM H. MULLER (Closing).—I think Dr. Varco is to be congratulated for this outstanding method of treating patients with pulmonic stenosis.

THE USE OF ENZYMATIC AGENTS IN THE DÉBRIDEMENT OF BURN AND WOUND SLOUGHS

JAMES F. CONNELL, JR., M.D., (BY INVITATION) AND
LOUIS M. ROUSSELOT, M.D., D.M.S., NEW YORK, N. Y.

(From the Department of Surgery, St. Vincent's Hospital, New York, N. Y., and New York University College of Medicine)

NUMEROUS proteolytic enzymes have been developed and employed in the débridement of wounds. The more important in clinical use, papain,[1] pepsin,[2] and trypsin,[3] have been attended with some local toxicity and inconstant success. Recently dialysates obtained from cultures of clostridia,[4] coliform,[5] pseudomona[6] and streptococcal[7] organisms have demonstrated powerful lytic activity on various but specific substrates.

In this paper we are presenting our clinical observations on the proteolytic activity of the streptococcal enzymes on wound and burn sloughs. This study supplements investigations already reported by Tillett and associates.[8]

Streptokinase, or S.K., is an enzyme which appears to catalyze the transformation of plasma plasminogin to plasmin, an active fibrinolysin in human plasma. This reaction takes place in a matter of minutes as measured by its lysis of a plasma clot in a pH range from 7.0 to 8.5 at 37.5° C. S.K. is readily soluble in water and saline or Zephiran solutions and its activity at body temperature lasts 20 to 24 hours. Proteolysis by this enzyme of fibrinous material requires the presence of serum and requires that the pH of the exudate be kept in the optimal range. To maintain continuous activity, acid exudates may require that the enzyme be suspended in a N/10 phosphate buffer.

The second enzyme, streptodornase or desoxyribonuclease, further designated as S.D., liquifies desoxyribose nuclear protein. Exudates with this protein are characterized by a stringy viscid coagulum. Since Sherry, Tillett, and Christensen[9] demonstrated that desoxyribose nuclear protein constitutes from 30 to 70 per cent of the total sediment in exudates, the proteolytic action of this enzyme assumes significance. It has no fibrinolytic activity. For optimal efficiency it requires a pH similar to that of S.K.

These enzymes act selectively on the specific substrates mentioned. Both enzymes are present in the concentrate as they have not been completely separated. The minimal concentrations required to expedite slough removal have not yet been determined. To date, 20,000 units per cubic milliliter of S.K. and 7 to 10,000 units per cubic milliliter of S.D. diluted in suitable menstruums have worked satisfactorily.

Except for an occasional hyperthermia with or without a preceding chill and transient nausea, no toxic manifestations have been noted to date.

Work performed under contract with the Office of Medical Research and Development, United States Army.

Enzymes used in this study were furnished through the courtesy of Lederle Laboratories, Division of American Cyanamid Co., New York, N. Y.

Read at the meeting of the Society of University Surgeons, Durham, N. C., Feb. 8-10, 1951.

MATERIALS AND METHODS

Patients with wounds complicated by the presence of slough were selected from the surgical service of the St. Vincent's Hospital, New York, N. Y. Patients with burns were obtained from the emergency service as they were admitted to the hospital. An attempt was made to study patients with 2 or more lesions so that one could be used as a control. To date, 12 burns and 21 wounds have been studied.

Before treatment was instituted each lesion was photographed, cultured, measured, and the pH and sediment of the exudate noted. After the first extremity burn had been immersed in a saline solution of the enzymes as described by Tillett and associates it was apparent that this technique was not suitable for surface lesions. First, the enzymes did not penetrate the thick slough, and second, a viscid medium was needed as a vehicle. The first problem was solved[10] by incisively crosshatching the thick slough into 3 by 5 mm. squares. The sharp surgical incisions were carried down to active viable tissue. The active inflammatory reaction at this interface contains the susceptible specific substrates among the collagen fibers.[11, 12, 13] The light bloody ooze resulting from the incisions provided the serum necessary for enzyme activity. The second need, that is, the use of a viscid menstruum, was met by the incorporation of Lubofax,* a water-soluble base. Where active suppuration was a concomitant factor the bacterial flora and its sensitivity to a variety of antibiotics was determined. The enzyme-antibiotic containing gel was then liberally spread over the wound surface. Fine mesh gauze impregnated with Xeroform or petroleum jelly was applied to act as a mechanical barrier to prevent diffusion of the active materials. All burns were treated on the fourth or fifth day postburn after fluid balance and normal hemogram had been attained.

All abscess cavities or sinus tracts were intubated with catheters and volumetric changes were measured daily. The enzymes, dissolved in normal saline solution, in 1:5000 solutions of Zephiran Chloride, or in Lubofax gel, were instilled daily, every few hours, or as a constant drip. The method selected was to insure the enzymes coming in contact with the wound surface for at least 24 hours. When the cavity filled in and the culture revealed no pathogenic organisms the tube was withdrawn and the wound allowed to close. In extensive ulcers and wounds, skin grafting was employed as soon as the slough was removed and the bacterial flora controlled. All patients were on systemic supportive therapy and their weight and hemograms were carefully followed.

RESULTS

Our results in this series of 33 patients are summarized in the following table.

As a sequel to this selected cases will be presented to demonstrate more adequately enzyme activity and efficacy.

Burns.—T. W., a 27-year-old Negro man, sustained third degree thermal burns of both legs. The initial treatment consisted of systemic supportive therapy, gentle lavage with

*Preparation manufactured by Burroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y.

TABLE I. RESULTS IN WOUNDS TREATED

TYPE	NO.	E	G	F*	U.I.†	CONTROLS
Burns						
Second degree	7	5	2	0	0	2
Third degree	5	3	2	0	0	4
Ulcerations	8	5	0	3	0	4
Postoperative wound infections	8	2	4	0	2	6
Large abscesses	3	2	0	1	0	2
Pleural cavity lesions						
Hemothorax	1	1	0	0	0	0
Fibrinous thorax	1	0	1	0	0	0
Totals	33	18	9	4	2	18

*Fair.
†Unimproved.

detergents, Xeroform gauze, and pressure dressings. The area of third degree burn was approximately 15 per cent of the total body surface.

On the fifth day postburn the primary dressing was removed in the operating room.

It was seen that the left leg was more extensively damaged than the right leg. Both legs were edematous, rubbery, dry and insensitive. The severely burned left leg was treated with the enzymatic agents and the right leg with pyruvic acid paste in the manner described by Connor and Harvey.[14]

The area clinically representing third degree burn of the left leg was extensively crosshatched to a depth of 1.5 to 2.0 cm. The leg was incased in a pliofilm bag and 300 c.cm. of normal saline solution with 20,000 units of S.K., 7,000 units of S.D., and 400 μg. of chloramphenicol per cubic centimeter were instilled.

The right, or control leg, was crosshatched over the lower medial surface. A liberal amount of freshly prepared pyruvic acid-starch paste was spread over the burned area and covered with an occlusive dressing. The dressings were changed daily and freshly made acid paste applied.

On the fourth day of treatment the left leg demonstrated that large areas of slough had separated en bloc over the anterior lower third and posterior aspects of the limb. Those blocks still present were held by strong collagen fibers which were atraumatically sectioned. Dressing was nonpainful, and there were no untoward reactions to the enzymes or paste.

On the sixth day the control leg revealed that some of the crosshatched slough, aided by extensive traumatic mechanical débridement of the viscid coagulum, had separated. Where crosshatching was not carried out, firmly adherent slough was present.

On the eighth day the leg treated with enzymatic agents revealed that all the slough was removed except for a narrow band that had not been exposed to the enzyme medium.

On the tenth day the enzyme-treated leg was ready for grafting and was covered with Xeroform gauze and a light, occlusive pressure dressing. The control leg still had many areas of adherent slough present. The application of pyruvic acid paste and the mechanical débridement was continued for 7 more days.

On the seventeenth day after the start of treatment the slough still adherent to the control leg was débrided and skin grafting of both limbs was carried out. The time for complete separation of slough by the enzymes was 6 days, while on the control leg the slough had not completely separated by the seventeenth day. The initial take of the grafts was recorded as 85 per cent for the enzyme débrided limb and 55 per cent for the control limb.

Discussion.—The slough produced by a deep thermal burn has for its predominate substrate a denatured collagen. Binding this slough to viable tissues are thick bands of collagen, fibrin, and cellular coagulum. The streptococcal enzymes are active as proteolytic agents only on the fibrinous and cellular coagulum. They have no lytic action on collagen or normal cells. The

lysis of the fibrinous coagulum in the meshes of the collagen strands has loosened the small blocks of slough and thus permitted atraumatic nonpainful excision to be carried out. To date, our third degree burns have had the slough removed

Fig. 1.

Fig. 2.

Fig. 1 (Patient T. W.).—Third degree thermal burns of lower extremities.
Fig. 2 (Patient T. W.).—Fourth day of enzyme therapy. Note crosshatched sections of slough.

Fig. 3.

Fig. 4.

Fig. 3 (Patient T. W.).—Eighth day of enzyme therapy, portion of limb exposed to enzymes is free of slough.

Fig. 4 (Patient T. W.).—Twelfth day of enzyme therapy, enzyme-treated limb in foreground is ready for grafting. Control limb still contains firmly adherent slough.

in 4 to 6 days. The wounds were ready for grafting in 8 to 14 days after incurring the burn. Healthy granulations with low bacterial counts were evident as soon as the slough was removed. There seems to be no inhibiting effect on cell migration, for there is rapid epithelization in the presence of the enzymes.

Fig. 5.

Fig. 6.

Fig. 5 (Patient J. L.).—Second and third degree burn of forearm.

Fig. 6 (Patient J. L.).—Ninety-six hours after start of enzyme therapy. Note the rapid epithelization in progress.

On deep second degree lesions the viscid, tenuous strands of slough separated quickly and islands of epithelium rapidly proliferated and coalesced. The enzyme-treated lesions were 72 to 96 hours ahead of the controlled group.

The optimal treatment of the third degree thermol burn slough awaits the development of an enzyme or enzymes that will act on the specific collagen substrates making up the slough.

Fig. 7.

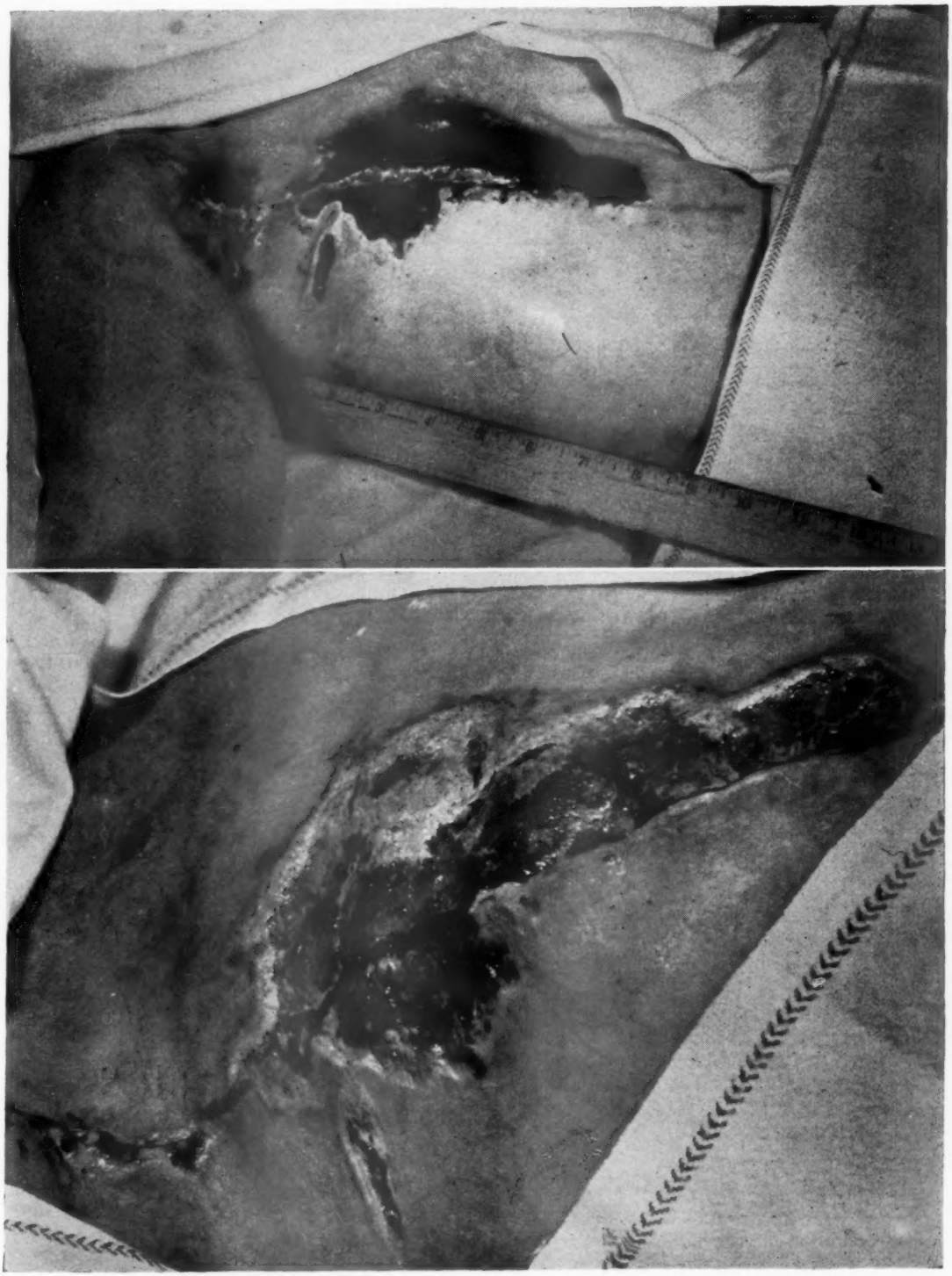

Fig. 8.

Fig. 7 (Patient S. G.).—Postoperative wound slough secondary to tension. Slough over anterior axillary line left untreated.

Fig. 8 (Patient S. G.).—Sixth day of treatment prior to surgery. Note migration of epithelial elements. Untreated slough is wet, tenuous, and adherent.

Postoperative Wound Infections.—S. G., a 56-year-old woman, had had a radical mastectomy performed for scirrhous carcinoma of the breast with primary closure of the wound. Subsequently the skin flaps underwent a slow progressive necrosis.

On the twenty-third postoperative day the firmly adherent wound slough was seen to encompass a 17 by 6 cm. area over the right thorax. Hemolytic *Staphylococcus aureus*, sensitive to aureomycin, was reported growing in the cultures. The slough was crosshatched down to the reddened base. S.K.-S.D. in Lubofax paste combined with 3 per cent aureomycin ointment was applied to the incised slough. A small area over the anterior axillary line was left untreated. No systemic antibiotic therapy was employed.

By the third day 70 per cent of the slough separated en bloc or was atraumatically débrided. Culture on the third day revealed a few colonies of nonhemolytic *Staph. aureus.* The control area of slough showed no separation, only a wetting reaction to the Lubofax-aureomycin ointment.

On the fifth day of treatment the wound surface was clean and islands of epithelium were spreading out rapidly. Culture revealed no growth of organisms. The wound was successfully grafted.

Discussion.—The postoperative wound sloughs are secondary to hematoma, traumatic handling of the tissues, septic contamination of the wound, or excessive tension. Local organisms liquify the fibrin clot, further destroy adjacent tissues, and cause a cellular reaction that may lead to abscess and slough formation. In such a situation a large portion of the materials formed are substrates susceptible to the proteolytic action of the enzymes. The thorough removal of nutrient debris by the enzymes quantitatively lowers bacterial flora. In all of the 8 lesions treated slough was removed and the bacterial flora reduced within 2 to 96 hours. Hematomas were lysed in 8 to 12 hours. Failure of the enzymes to débride 2 postoperative wound sinus tracts of long duration was due to the presence of substrates outside their range of activity.

Ulcerations.—J. G., a 53-year-old man with traumatic quadriplegia, developed a sacral decubitus ulcer with a burrowing sinus tract into the right buttock 45 days after injury. At 90 days 3 more lumbar decubitus ulcers had appeared.

The sacral lesion had been unroofed but was badly infected. The sinus tract was full of exudate and lined by necrotic tissue. All 3 areas of slough over the lumbar region were carefully crosshatched. The middle lumbar and sacral lesions were treated with S.K.-S.D. in Lubofax with 3 per cent aureomycin ointment added to the gel. The left lumbar decubitus ulcer received no therapy. The right lumbar lesion was dressed daily with a Lubofax-aureomycin ointment. Culture of these lesions revealed the presence of *Proteus vulgaris* and gamma streptococci.

By the end of 48 hours granulations were evident in the base of both treated lesions. The exudate was thin and the odor decreased.

On the seventh day granulations were filling in the treated wounds. However, the necrotic ligamentous tissue between the spinous processes was unaffected and had to be mechanically débrided. The sinus tract was filling in rapidly. The maceration attending the profuse drainage previous to treatment disappeared.

On the sixteenth day of treatment the firm red granulations were covered with split-thickness skin grafts. The sinus tract was completely obliterated. The untreated control lesion was separating at the periphery and the control lesion, subjected to constant wetness, had separated off one-half of its superficial slough.

Discussion.—Ulcerations in various anatomic sites and secondary to ischemia and denervation apparently have sloughs of various collagenous substrates. Where secondary infection is a concomittant factor the slough and exudate are

Fig. 9.

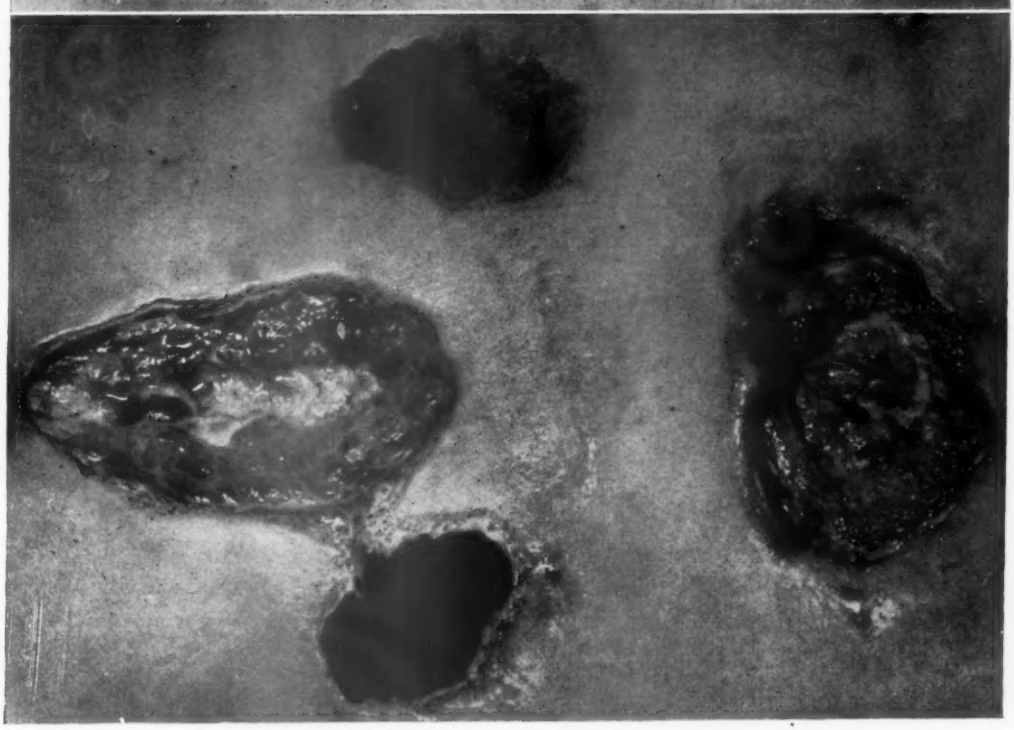

Fig. 10.

Fig. 9 (Patient J. G.).—Note crosshatched slough of decubiti; midline lesions and sinus tract treated with enzymes. Lesion in foreground is untreated. Lesion in background is exposed to enzyme-free vehicles.

Fig. 10 (Patient J. G.).—Seventh day of treatment. Granulations are filling in both treated wounds. Note collagenous interspinous ligament slough.

Fig. 11. Fig. 12. Fig. 13.

Fig. 11 (Patient H. W.).—Right intubated subphrenic abscess. Volume measured as 110 c.c.
Fig. 12 (Patient H. W.).—After 20 days of treatment, wound volume measured 27 c.c.
Fig. 13 (Patient H. W.).—At 43 days wound volume measured 10 to 12 c.c.

in the substrate spectra of the streptococcal enzymes. Many of the ulcerations with adherent coagulum and slough had been previously treated with wet soaks of the usual materials with little effect. In 6 of the 8 lesions treated with S.K.-S.D. the slough was dramatically removed in 48 hours. In 72 hours the granulating surface was clean and sterile.

Large Abscess Cavities.—H. W. (third admission), a 35-year-old Negro man, 7 days prior to treatment with the enzymes had 1300 c.c. of purulent exudate drained through a posterior extrapleural approach. Sixteen and one-half months prior to this a perforated duodenal ulcer had been closed in the usual manner. The culture of peritoneal fluid was sterile and the patient, after an uneventful recovery, was discharged on the third day. Thirteen months later the patient developed intermittent pain in the left flank, chest pain, and a productive cough. Symptomatology became progressively more debilitating and he was admitted to the hospital after 3 days of chill and fever. Weight loss of 27 pounds occurred in the 4 months prior to admission.

On admission a roentgenogram revealed a markedly elevated left diaphragm. No electrocardiographic changes were noted. Culture of the pus obtained at operation revealed *Alkaligenes fecalis,* sensitive to Chloromycetin. The pH of the exudate was 7.5. On the seventh day postdrainage wound volume measured 110 c.c. The enzymes in 90 c.c. normal saline solution were introduced daily through a catheter. Wound volume quickly reduced in size, but it was found that loculation was occurring. However, the concentration of the enzymes was increased and the loculations broke down spontaneously. This occurred 3 times in the course of therapy. The exudate remained thin and watery, with very few organisms.

At 20 days the volume had been sharply reduced to 27 c. ml. and the patient had gained 10 pounds.

At 43 days the wound volume was 10 to 12 c.c. and the exudate was sterile.

At 50 days therapy was halted, as just a simple 6 cm. tract remained. The catheter was gradually pulled out and the wound closed by the fifty-fourth day. During the 50 days of therapy the patient gained 27½ pounds and exhibited no toxic manifestations.

Discussion.—Large chronic abscesses of long duration have a thick, necrotic, fibrinous wall that is covered with slough and filled with seropurulent exudate and gas. These substances have substrates susceptible to the proteolytic activity of the streptococcal enzymes. In instances where the organism has been of low virulence and the tissue reaction fibroblastic the thick wall is predominately collagenous and enzyme action is restricted. However, the thinning of the viscid exudate, the decrease of bacteria, and the removal of susceptible slough brings about a collapse of the cavity, proliferation of granulations, and eventual extrusion of the collagenous slough. To date the large abscesses have healed more rapidly, and without any residual sinus tracts, in treated cases than in untreated controls.

SUMMARY

1. The enzymes streptokinase and streptodornase, derived from streptococcal organisms, have proved to be effective in the lysing of susceptible portions of wound exudates and sloughs in a variety of surgical lesions.

2. The streptococcal enzymes to aid in the atraumatic separation of slough must have the proper substrates present as part of the slough-tissue separation reaction.

3. It is quite apparent in our studies that many different substrates go into the make-up of various slough and these substrates will require the proper proteolytic enzyme system for lysis.

4. In burn and wound sloughs it has been necessary to crosshatch the slough for the enzymes to reach their specific substrates.

5. Collagenous material, epithelial cells, and fibroblastic cells are not in the spectra of the proteolytic activity of S.K. and S.D.

6. The enzymes must be replenished at least every 24 hours, or earlier, depending on the amount of concomitant exudate-transudate elaborated by the lesion.

7. Local use of antibiotics may be justified as the dead tissue foci are removed.

8. No serious local or systemic toxic manifestations were noted.

REFERENCES

1. Glasser, T.: New Treatment for Sloughing Wounds, Am. J. Surg. **50**: 320, 1940.
2. Howes, E. L.: Treatment of Wounds and Burns, New York State J. Med. **44**: 2006, 1944.
3. Stucke, K.: Has Digestion of Slough by Pancreatic Ferments Been Found Valuable in Treating Severe Burns? Chirurg. **20**: 588, 1949.
4. MacLennon, J. D.: Preparation and Action of Collagenase. Read at Halsted Club, December, 1950.
5. Altemeier, W. A.: Enzymatic Débridement of Wound Slough. Read at Halsted Club, December, 1950.
6. Idem.
7. Tillett, W. S.: The Fibrinolytic Activity of Hemolytic Streptococci, Bact. Rev. **2**: 161, 1938.
8. Tillett, W. S., and others: Streptococcal Enzymatic Débridement, Ann. Surg. **131**: 12, 1950.
9. Sherry, S., Tillett, W. S., and Christensen, L. R.: Presence and Significance of Desoxyribose Nucleoprotein in the Purulent Pleural Exudates of Patients, Proc. Soc. Exper. Biol. & Med. **68**: 179, 1948.
10. Connell, J. F., Jr., and Rousselot, L. M.: Enzymatic Agents in the Débridement of Wound and Burn Sloughs (Preliminary Report), National Research Council, November, 1950. To be published.
11. Elman, R., and Lischer, C.: The Local Skin Lesion in Experimental Burns and Its Relation to Systemic Manifestations, Surg., Gynec. & Obst. **78**: 364, 1944.
12. Moritz, A. R.: Studies of Thermal Injury: III. The Pathology and Pathogenesis of Cutaneous Burns; An Experimental Study, Am. J. Path. **23**: 915, 1947.
13. Entin, M. A., and Baxter, H.: Experimental and Clinical Study of Histopathology and Pathogenesis of Graduated Thermal Burns in Man and Their Clinical Implication, Plast. & Reconstruct. Surg. **6**: 352, 1950.
14. Connor, G. J., and Harvey, S. C.: The Pyruvic Acid Method in Deep Clinical Burns, Ann. Surg. **124**: 799-810, 1946.

DISCUSSION

DR. EDWARD STAFFORD.—I have observed a number of patients treated with these enzymes with a great deal of interest. I would like to compliment the author on the presentation first. Of course, when any person becomes interested in the care of wounds, he soon begins to get better results with those wounds no matter what method he is using. I think that the surest evidence we have of the effectiveness of streptokinase and streptodornase is in the hemothoraces, where the blood disappears like magic. A second group where we found very good results are patients who have tuberculosis, tubercular empyema, cold abscesses, or sinus tracts, which after a few days of treatment with these materials can actually be closed as one would do a secondary closure on any clean wound with good healing. There are a few tricks in its use. You have heard some of them mentioned. We have found that a satisfactory

way of handling sinus tracts or open wounds is after application of the material, to cover the wound with sheet rubber or a portion of a rubber glove and cement that to the skin surface to keep the enzymes in contact with the wound.

DR. EUGENE CLIFFTON.—I hesitate to get long-haired but it is well konwn that this is a very complicated enzyme system and that actually many of the variations in results depend on the variations within the individuals themselves and in their exudates at the time the enzyme is used. There are several factors that are effective. The individual patient may have a marked variation in the plasminogen in his own blood stream which will affect the amount in the exudates. There is also a significant variation in the antiproteolytic reaction in the blood stream and in these exudates. If one would test at the beginning the amount of plasminogen that is contained in the exudates or in the blood, one could accurately estimate how much streptokinase to use in order to get the maximum activity and not endanger the patient with a severe reaction. Occasionally, when putting this material into a pleural cavity full of blood, one will get a very severe reaction if that patient has a quantity of plasminogen in his blood. The variations can be as great as 10 to 1 so far as the activity is concerned. This can be tested by ordinary proteolytic and fibrinolytic methods. Another factor that enters into the reaction is the amount of antistreptokinase that may be present in the serum or exudate. If the patient has had a previous streptococcal infection, he may have a very high antistreptokinase and no matter how much streptokinase is used his plasminogen will not be activated. Then staphylokinase or one of the other kinases might very well activate that plasminogen.

DR. JAMES F. CONNELL (Closing).—We now have a very simple test for evaluating the patient's fibrin sensitivity to streptokinase. Three cubic centimeters of whole blood are collected from the patient, put in a blood plate, and allowed to coagulate. Small paper discs impregnated with various concentrations of streptokinase and streptodornase are then applied to the surface of the blood clot. Generally within 30 minutes to 2 hours a very definite lysis of the blood clot around the little paper discs will occur.

OBSERVATIONS ON THE CIRCULATORY EFFECTS OF SHORT DURATION POSITIVE PRESSURE PULMONARY INFLATION

GERARD TAYLOR, M.B., F.R.C.S. (ENG.), AND FRANK GERBODE, M.D.*
SAN FRANCISCO, CALIF.

THE development of thoracic surgery has depended to a large degree on the better understanding of the problems of anesthesia with an open chest, for with the lung exposed to atmospheric pressure, some method of positive pressure inflation must be used to ensure adequate respiratory exchange. Continuous insufflation has long been abandoned, and in modern practice the lungs are intermittently inflated mechanically[1, 2] or manually. For the most part, low pressures well within the range of safety are used, the anesthetist being well aware of the dangers of overinflation; but occasionally, as in re-expansion of the lung during a lengthy thoracic procedure, the anesthetist may be asked to apply moderate or high pressures so that all areas of atelectasis are removed, and a similar technique is often employed at the completion of a thoracic operation. Also, when acute respiratory or cardiac failure occurs, the urgency of the moment may inadvertently lead to the use of unnecessarily high pressures for artificial respiration.

It is the purpose of this paper to review briefly the previous studies of the dangers of positive pressure pulmonary inflation and to re-examine the possible adverse effects of short duration overinflation of the lungs, with particular reference to the mechanism of the circulatory depression produced by such a procedure.

Among the hazards of positive pressure inflation of the lungs, there are three which are outstanding. Two of these, namely the production of air embolism and mediastinal emphysema, require much higher pressures than would be used in anesthesia. The third undesirable effect is circulatory depression, which can occur with the use of moderate inflation pressures.

AIR EMBOLISM

Air embolism resulting from overinflation of the lungs was investigated by several workers.[3-5] It was found that, in dogs, inflation pressures above 8 cm. of mercury produced rapidly fatal air embolism. The mechanism of death in such instances is quite different from that of the more widely known systemic venous air embolism where comparatively large quantities of air are required to impede cardiac function by a mechanical churning effect in the right ventricle. In pulmonary air embolism, the gas quickly reaches the arterial circulation, and a few bubbles only are sufficient to block the coronary or cerebral circulation. The high inflation pressure overdistends the lungs with rupture of the alveolar walls

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Read at the meeting of the Society of University Surgeons, Durham, N. C., Feb. 8-10, 1951.
*From the Laboratory of Experimental Surgery, Stanford University School of Medicine, and The Surgical Professorial Unit, St. Bartholomew's Hospital Medical School, London, England.

and pulmonary venules, and if this overdistention is prevented by supporting the chest wall, then higher pressures can be used without harm.[3] Conversely, in an unconscious subject or with the thorax widely opened, overdistention of the lungs can occur more easily, and damage may be produced by somewhat lower pressures. A conscious subject, in performing the Valsalva experiment of expiration against resistance, can support a column of mercury 15 cm. high because, in this instance, the forcible contraction of the expiratory muscles effectively splints the thorax and prevents pulmonary overdistention.

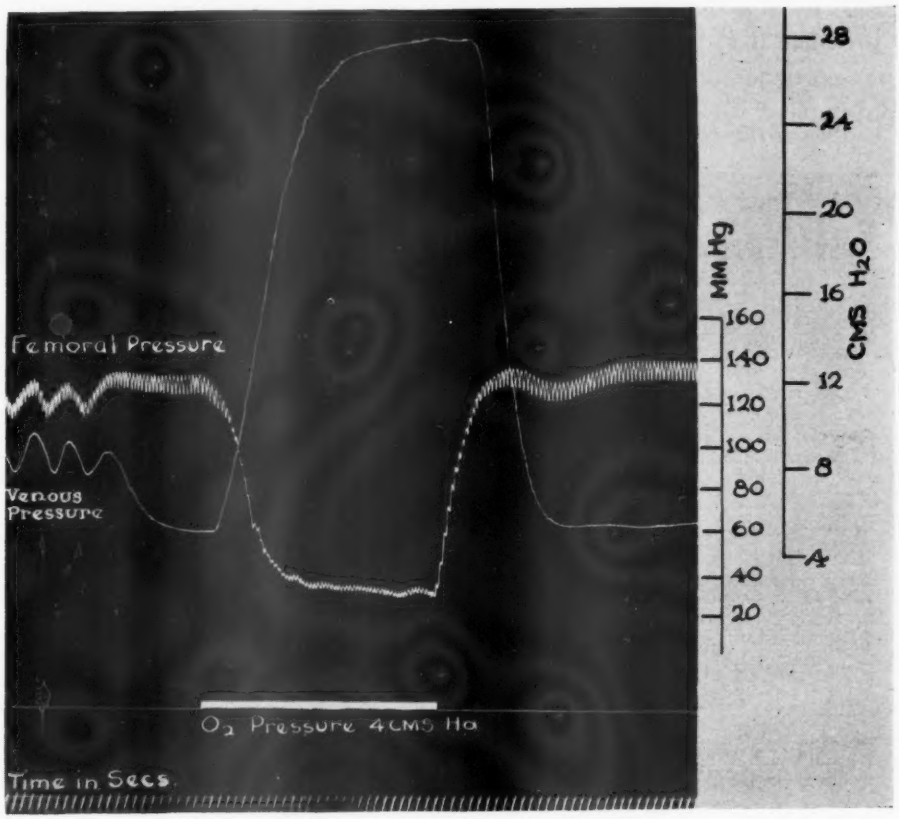

Fig. 1.—The lungs were inflated with oxygen at a pressure of 4 cm. Hg during the period indicated by the signal. The typical responses of the systemic arterial pressure and the jugular vein pressure in an animal with an intact thorax are shown.

MEDIASTINAL EMPHYSEMA

The research of Marcotte and associates[7] and Macklin[6] has shown that this complication of positive pressure pulmonary inflation may occur with pressures on the order of 20 mm. of mercury sustained for a period of thirty minutes. If higher pressures are used, mediastinal emphysema occurs more rapidly. The gas passes through the damaged alveolar wall, gains the perivascular space surrounding the pulmonary vessels, and hence reaches the mediastinum. When pneumothorax occurs as a result of positive pressure pulmonary inflation, the gas usually reaches the pleural space via the mediastinum, and direct rupture of the normal visceral pleura covering the lungs is rare. Many instances of

mediastinal emphysema following pulmonary inflation or prolonged forcible expiratory efforts have been reported, and the whole subject is presented in the extensive review by Macklin and Macklin.[8]

THE CIRCULATORY EFFECTS OF PULMONARY INFLATION

Essentially, inflating the lungs with a positive pressure of above 15 mm. of mercury produces a rise in external jugular vein pressure, a rise in pulmonary artery pressure, and a fall in cardiac output, which is manifested under certain conditions by a steep decline in systemic arterial pressure. The fall in systemic blood pressure is approximately proportional to the inflation pressure used, and the same sequence of events occurs in the Valsalva experiment where the rise in intrapulmonary pressure is produced by forcible expiration against resistance.

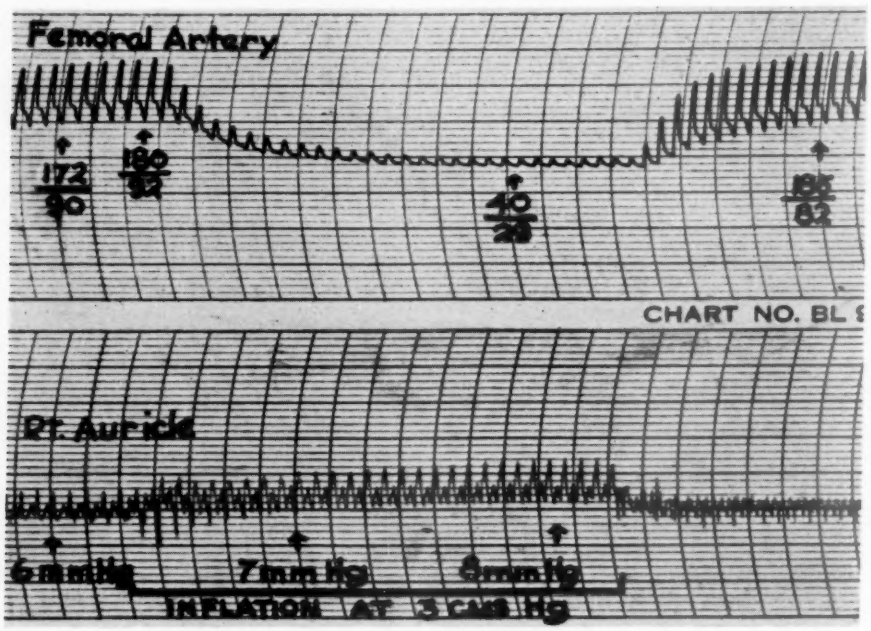

Fig. 2.—Strain gauge electromanometer recording of femoral artery pressure and right auricular pressure during a 14-second period of pulmonary inflation at 3 cm. Hg pressure. In this animal, the chest wall had been turned down and there was no tamponade. The progressive rise of right auricular pressure during inflation is due to commencing right ventricular failure.

The systemic arterial pressure curve during a period of acute increased intrapulmonary pressure exhibits five main features[9] (Figs. 1 and 2). The immediate response is a brief rise in systemic arterial pressure which has been explained as being due, first, to the transference of the increased intrathoracic pressure to all structures within the thorax including the heart and great vessels, and, second, to the mechanical squeezing out of blood contained in the pulmonary circulation into the left auricle. If the inflation pressure used is high enough, this initial rise is immediately followed by a precipitous fall in systemic arterial pressure which continues until reflex compensatory vasoconstriction enables a plateau to be developed. There may then be a slow recovery, but more

often the hypotension continues until the intrapulmonary pressure is released, when, after a short further drop, the blood pressure swiftly climbs back to a level above that which existed before inflation.

This overswing is of short duration and is due to the recovering cardiac output meeting the reflex vasoconstriction induced by the period of hypotension.[9] It is abolished by sympathectomy and has been used as an indication of sympathetic activity following operation for relief of hypertension.[10]

Our experiments confirmed the previous work on the production of air embolism and mediastinal emphysema, but our primary interest was to study the mechanism of the reduction in cardiac output which is indicated by the fall in systemic arterial pressure during pressure inflation of the lungs.

On a theoretical basis there are three possible explanations for the circulatory depression (Fig. 3). It may be due, first, to a vagal inhibitory effect acting directly on the myocardium, the afferent side of the reflex arc commencing in

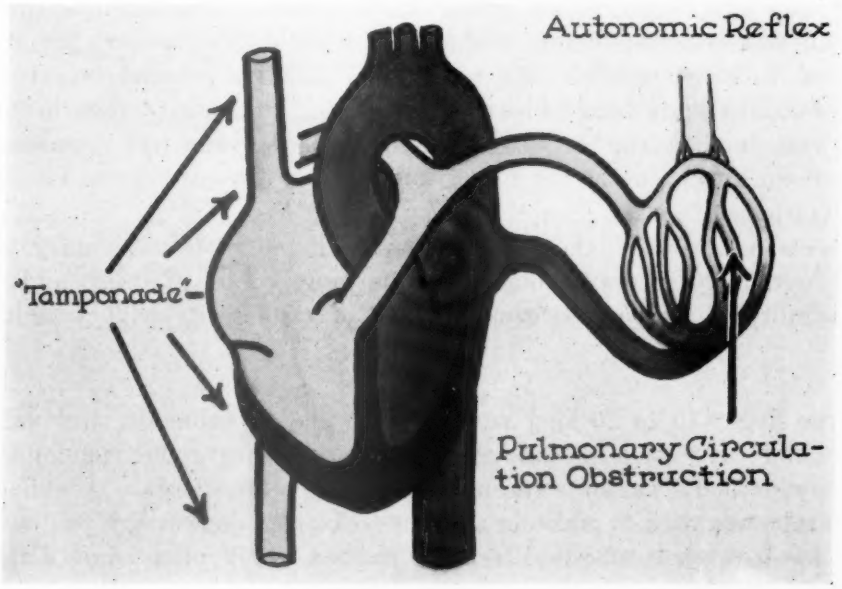

Fig. 3.—Diagram of the 3 possible mechanisms in the production of circulatory depression during pressure inflation of the lungs.

vagal receptors in the lung or aortic arch. It has been shown that stimulation of efferent vagal fibers produces a sudden fall in systemic blood pressure very similar to that produced by pressure inflation of the lungs.[11] However, previous work has demonstrated that vagal section and denervation of the aortic arch do not significantly alter the fall in systemic arterial blood pressure during inflation of the lungs.[9, 11-13]

Second, the expanding lungs may hinder the filling of the right ventricle by compression of the heart and venae cavae. This factor is generally held to be the most important one in producing circulatory changes during positive pressure pulmonary inflation, and has been called cardiac tamponade.[14] In previous papers published in support of this factor the final conclusions were

based on measurements of external jugular vein pressures in dogs during periods of positive pressure inflation of the lungs.[14-16] It was shown that if the venae cavae and heart were protected against compression during inflation by right pneumonectomy, then very little rise in external jugular vein pressure occurred. It was concluded that this absence of external jugular vein pressure rise when tamponade was abolished indicated that the circulatory effects were due to this factor. However, more recently it has been shown that the rise in peripheral venous pressure during pressure breathing may be fully compensatory in nature and that the effective venous pressure may be well maintained.[17]

The third factor which may act in decreasing left ventricular output during pressure inflation of the lungs is the obstruction of the pulmonary vascular bed by the high intrapulmonary pressure. For as soon as the intrapulmonary pressure exceeds atmospheric, then the peripheral resistance which the right ventricle has to overcome is increased; if this external pressure on the pulmonary capillary bed is great enough, then impairment of right ventricular emptying and left auricular filling would occur. Chillingworth and Hopkins[13] held that this factor was responsible for producing circulatory depression, but their investigation failed to exclude the tamponade factor adequately, and likewise Sharpey-Schafer and Bain[12] also concluded that the obstruction to the pulmonary vascular bed was the chief mechanism in reducing left ventricular output in pressure inflation of the lungs, but without any attempt to evaluate the role of tamponade.

It seemed necessary, therefore, to determine whether pulmonary vascular bed obstruction by pressure inflation of the lungs could, of itself, and without any possibility of tamponade, cause the fall of systemic arterial pressure.

METHOD

Large dogs (10 to 20 kg.) were used in the experiments, and data from approximately fifty such animals were obtained. Intravenous Nembutal (1 gr. per 5 pounds body weight) was used to produce anesthesia. A cuffed endotracheal tube was used to make an airtight seal, or a tracheotomy was performed and a wide bore glass tube tied into the trachea. A Y piece enabled the lungs to be connected either to a mechanical respirator pump or to a pressure reservoir containing oxygen or air. By adjusting these connections, the lungs could be inflated to any desired pressure for a given time. Pressures in various parts of the circulation were recorded by mercury and water manometers on a kymograph or by a direct ink writing strain gauge electromanometer.

In the observations on air embolism, airtrap cannulas of a similar type to those used by Van Allen and co-workers[4] were placed in peripheral arteries or directly into the left auricle.

It is necessary to emphasize that these observations are concerned with the effects of short isolated periods of positive pressure only, and inflation was limited to between 10 and 30 seconds' duration in most cases. These experiments will be described in the three groups.

The Production of Air Embolism.—Observations were made on ten animals in this group. Inflation for periods of 15 seconds was commenced at pressures

of 10 mm. of mercury and raised by 5 mm. steps until the production of air embolism was signalled either by the observation of bubbles in the airtrap cannulas placed in the femoral or carotid vessels or the sudden death of the animal. After death, immediate autopsy always revealed the presence of many tiny bubbles in the coronary arteries and fibrillation of the ventricles.

Van Allen's[4] observations on the effect of gravity in determining the pathway of the air bubbles which gain the arterial circulation were confirmed. Thus, if the hindquarters of the animal were raised, the gas bubbles appeared only in the femoral artery cannulas; several such inflations could be performed in the same animal without causing death. It was thought that once the lung had been damaged sufficiently to produce air embolism, subsequent emboli would be produced at lower inflation pressures, the tear in the alveolar structure being already present. To test this, three experiments were performed with the finding that this was not so, and the initial minimum inflation pressure required to produce air embolism for each individual animal had to be exceeded on every occasion before gas bubbles were observed in the peripheral vessels. The minimal pressures required to produce air embolism with a closed chest and with a widely open thorax are shown in Table I. Contrary to previous work, embolism did not occur at lower pressures when the lungs were allowed to overdistend through an open thorax.

TABLE I

INTACT THORAX		OPEN THORAX	
DOG NUMBER	MINIMUM PRESSURE PRODUCING AIR EMBOLISM (CM. Hg)	DOG NUMBER	MINIMUM PRESSURE PRODUCING AIR EMBOLISM (CM. Hg)
1	10	6	12
2	12	7	12
3	10	8	10
4	13	9	15
5	10	10	8

The duration of inflation in each experiment was 15 seconds.

Mediastinal Emphysema.—All the observations in this group were of necessity made with an open thorax so that the immediate occurrence of mediastinal emphysema would be noted. In all the experiments the duration of inflation was limited to between 10 and 30 seconds. Air was observed to gain the mediastinum at the lung root and in no case was rupture of the visceral pleura covering the lung noted. In experiments on four animals, the minmum pressure required to produce this complication ranged between 7 and 10 cm. of mercury, the average for the experimental series being 9 cm.

Circulatory Depression.—Observations on forty dogs were made in this group. Because of previous work which had used the rise in venous pressure as an indicator of circulatory depression,[15] it was felt advisable to study the relationship between the rise in external jugular vein pressure and the fall in systemic arterial pressure during positive pressure inflation of the lungs. Accordingly, pressures from the external jugular vein or superior venae cavae and the femoral artery were recorded on a kymograph during inflation of the lungs to 4 cm. of mercury for a period of 15 seconds.

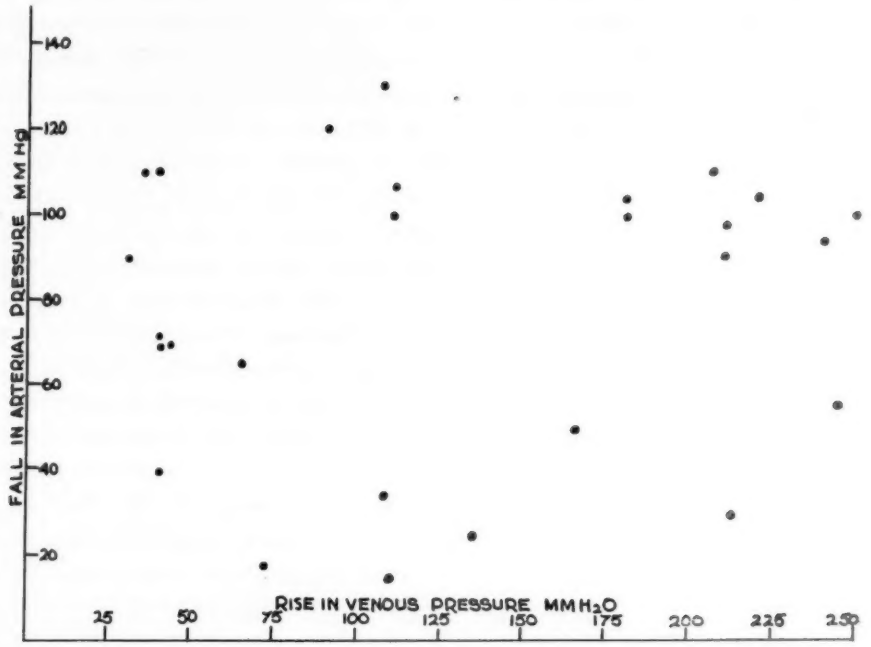

Fig. 4.—Rise in external jugular vein pressure and fall in systemic arterial pressure during inflation of the lungs at 4 cm. Hg pressure for 15 seconds, with an intact thorax. The results of 27 experiments, each in a separate animal, are shown, and it can be seen that there is no correlation between the venous and arterial pressure responses.

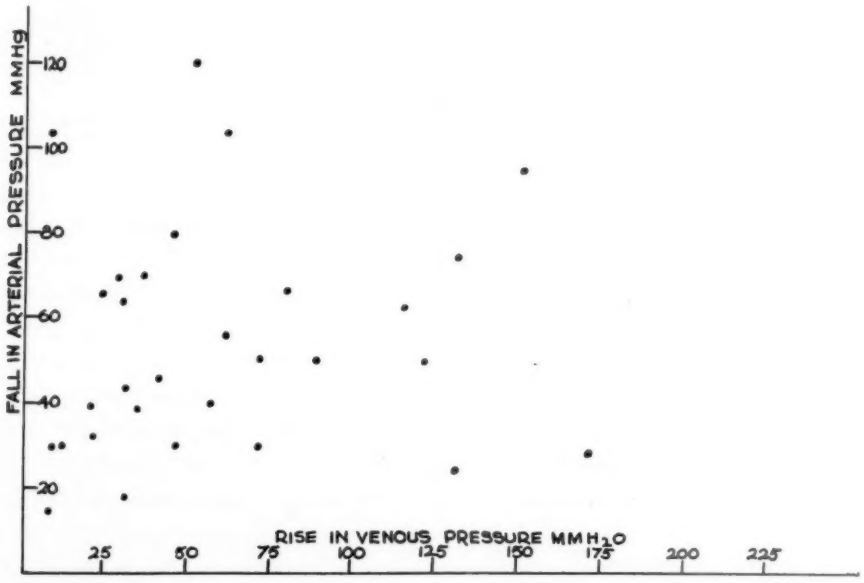

Fig. 5.—Rise in external jugular vein pressure and fall in systemic arterial pressure during pulmonary inflation to 4 cm. Hg for 15 seconds with a widely open thorax, or after right pneumonectomy. The results of 30 separate experiments are shown, and, although the venous pressure response is less than with a closed thorax (Fig. 4), the systemic arterial pressure fall still occurs.

The results of twenty-seven such observations in the anesthetized animal with a closed chest are charted in Fig 4. It can be seen that there is no constant correlation between the venous pressure rise and systemic arterial pressure fall.

Also, when the thorax was opened and the lungs were allowed to expand away from the mediastinum, or after right pneumonectomy, less rise in venous pressure was recorded, but a considerable fall in arterial pressure still occurred (Fig. 5).

It was therefore apparent that measurement of the venous pressure response to pulmonary inflation did not give an accurate indication of the systemic arterial pressure response. In fact, as will be described more fully later, it

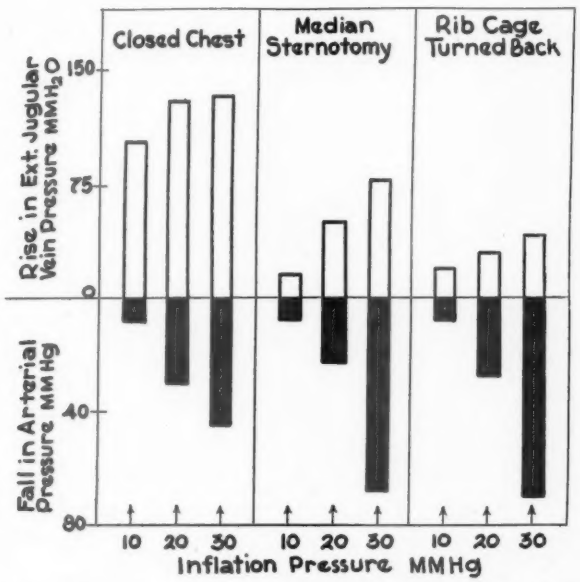

Fig. 6.—Effect of pulmonary inflation to 1, 2, and 3 cm. Hg for 15-second periods on the systemic arterial pressure and external jugular vein pressure in the same animal with the thorax intact, after a median sternotomy had been performed, and after the rib cage had been turned back. It can be seen that when tamponade had been minimized, there was less rise in venous pressure, but the fall in systemic arterial pressure persisted.

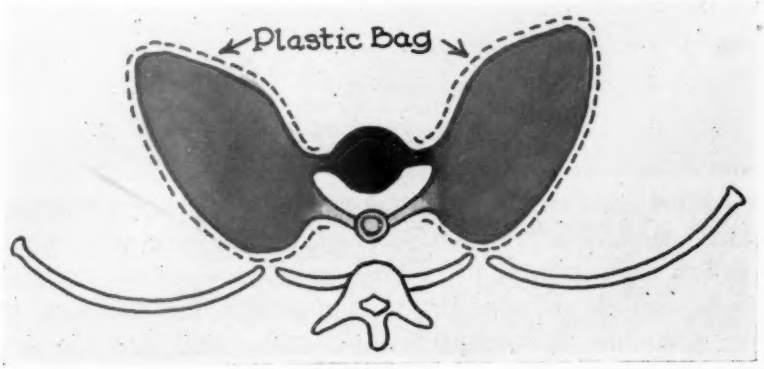

Fig. 7.—Diagram of the experimental preparation devised to avoid compression of the mediastinum during pulmonary inflation. A median sternotomy is performed and the ribs are divided close to the spine. The rib cage is then turned back, leaving the lungs and mediastinum free. The lungs are enclosed in bags of thin plastic material to prevent overdistention.

was noted that in the same animal, equally great falls in systemic arterial pressure were seen when steps had been taken to avoid tamponade and when the venous pressure response to inflation was minimal (Fig. 6).

It is worth while emphasizing that although the fall in systemic blood pressure is a better indicator of the drop in cardiac output during pressure inflation under anesthesia than the rise in venous pressure, it is in fact only an indicator. The peripheral resistance is the other factor capable of influencing the fall in blood pressure. This, obviously, will not remain constant during a

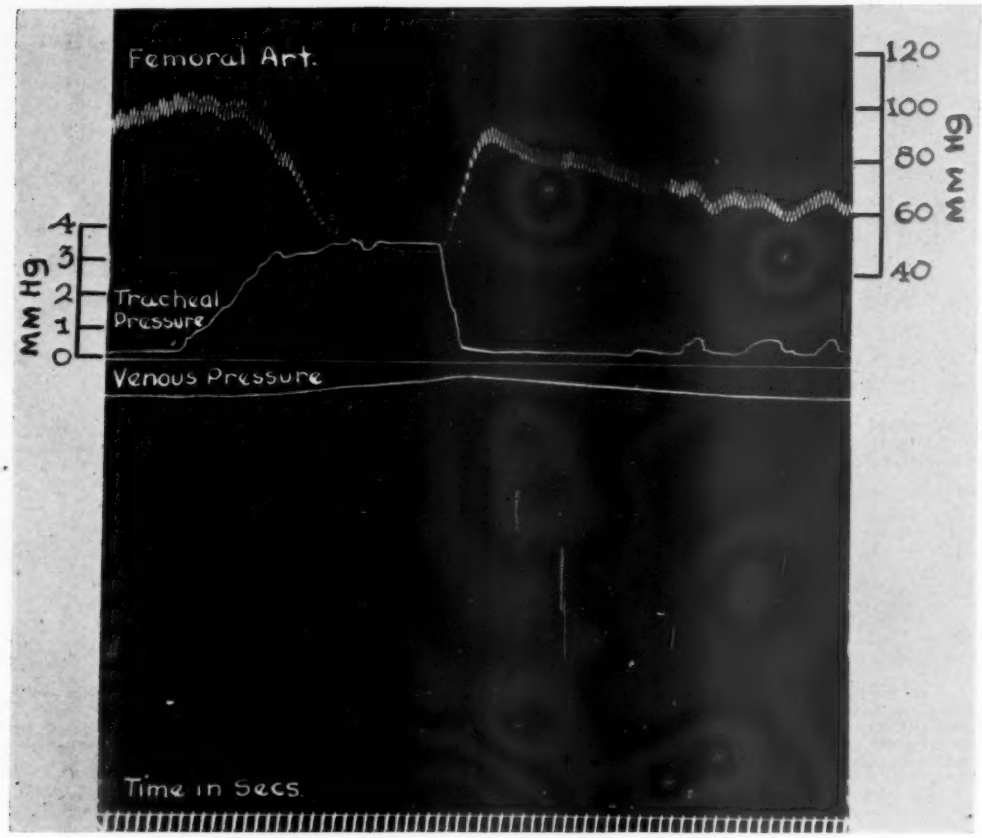

Fig. 8.—Effect of pulmonary inflation on femoral artery and external jugular vein pressure in the experimental preparation shown in Fig. 7. With the absence of tamponade, there is little rise of external jugular vein pressure, but a fall in femoral artery pressure still occurs.

long and surgically extensive experiment, and it is therefore only correct to compare quantitative measurements of the fall in systemic blood pressure if they have been recorded from the same animal within a very short space of time. In evaluating our results, this criterion was kept in mind and conclusions were not drawn unless the experimental procedures were consecutive.

In order to exclude all possibility of tamponade, the following preparation was devised: A median sternotomy was performed and then the second to the ninth ribs on each side were divided close to the spine posteriorly (Fig. 7). In this way, the chest wall could be turned down like the leaves in a book, leaving the lungs and medastinal structures free. The lungs were enclosed in bags of

plastic material to prevent overdistention, and so that they could be retracted gently from the mediastinum. Blood transfusions were given during the procedure so that the animals remained in good condition with well-maintained blood pressure. Great care was necessary during subsequent inflation to prevent mediastinal shift and mechanical kinking of the venae cavae. It was found that the lungs could be inflated in this preparation without any compression

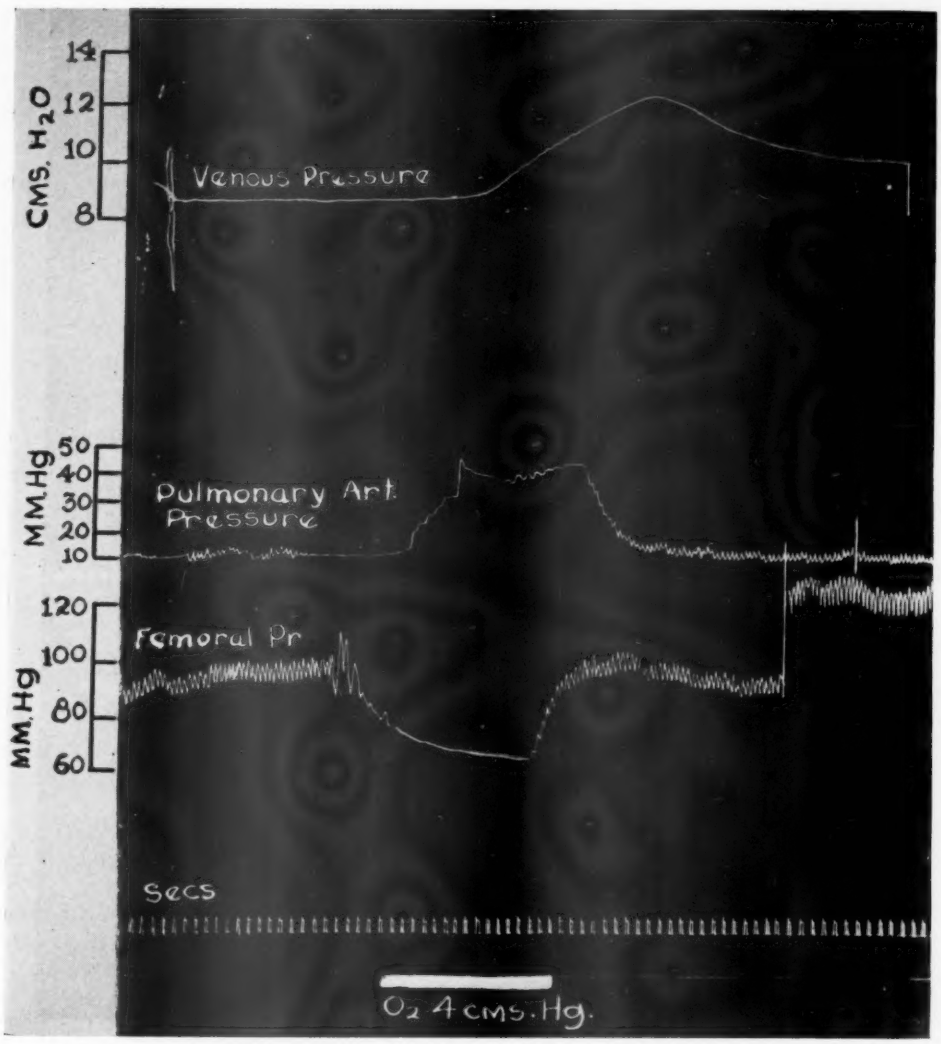

Fig. 9.—Pulmonary inflation to 4 cm. Hg pressure as indicated by signal. There is a fall in femoral artery and a rise in pulmonary artery pressure (Fig. 11).

of the mediastinal structures. Very little rise in external jugular vein pressure resulted, but a substantial fall in systemic arterial pressure still occurred. Fifteen such experiments were performed with a consistent response. A representative tracing from one of these preparations is shown in Fig. 8. All the subsequent experiments to be reported were performed on such a preparation so that tamponade could be avoided.

Concomitantly with the fall in arterial blood pressure during periods of inflation, there was a rise in pulmonary artery pressure (Fig. 9). However, when artificial compression of the venae cavae was produced by partial clamping, thus hindering the return of blood to the right ventricle sufficiently to cause a fall in systemic arterial pressure, there occurred also a fall in pulmonary artery pressure (Fig. 10).

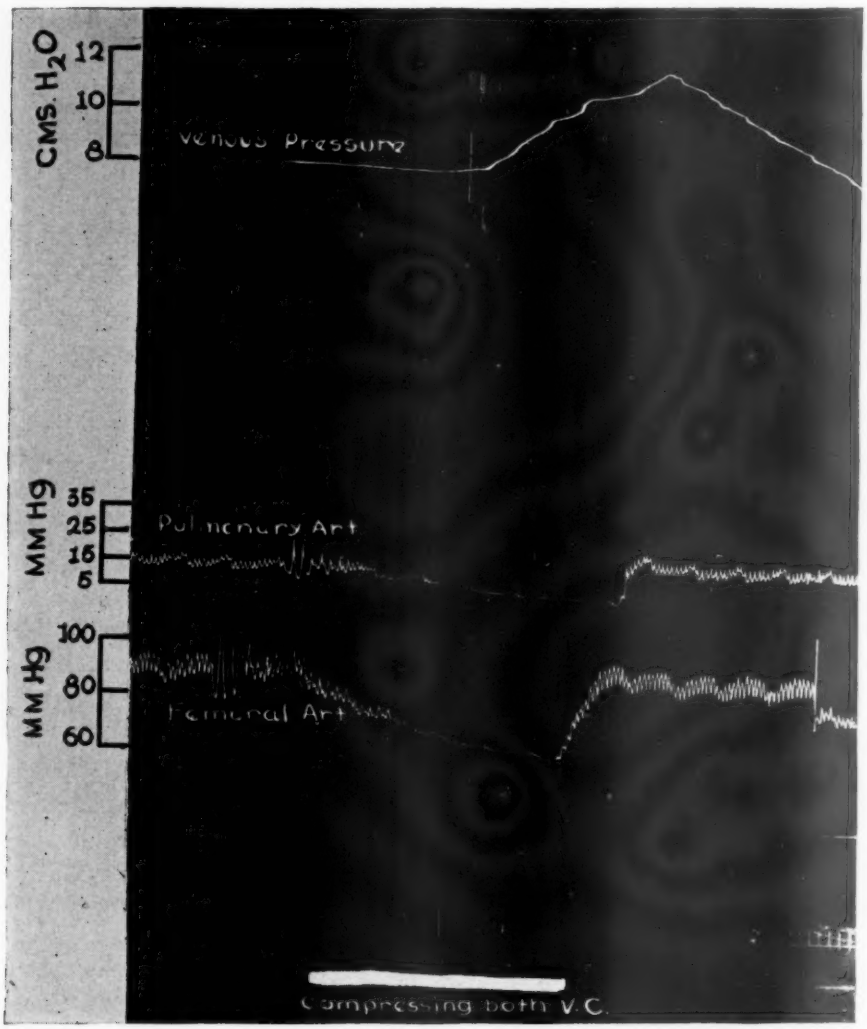

Fig. 10.—Effect of producing "artificial tamponade" by partial constriction of both venae cavae during the period indicated by the signal. A fall in both femoral artery and pulmonary artery pressure is seen.

From these experiments, it was, therefore, apparent that even with tamponade excluded, some factor was operating to cause a reduction in left ventricular output, and it appeared likely that obstruction of the pulmonary vascular bed as indicated by the rise in pulmonary artery pressure was responsible for this circulatory depression. To prove this, it was thought that if some way of bypassing the obstructed pulmonary circulation during periods of pulmonary in-

flation could be devised, then little or no fall in cardiac output, as indicated by a decline in systemic arterial pressure, would occur. As one lung is adequate to maintain sufficient pulmonary circulation,[18] the following preparation was used: a clamp was placed on one main bronchus so that when positive pressure was applied to the tracheal tube, the opposite lung only would be distended (Fig. 11). In this way, a free circulatory pathway through the undistended lung was available during the period of pulmonary inflation and the transference of the blood from the right ventricle to the left auricle was relatively unimpeded. The recordings of such an experiment are shown in Figs. 12 and 13. It can be seen that if a free pulmonary vascular pathway was maintained during inflation, then the systemic arterial blood pressure is little effected. In order to confirm the role of the pulmonary vascular pathway, this experimental preparation was modified by clamping the pulmonary artery of the undistended lung (Fig. 14). This eliminated the free pathway through the undistended lung and the usual fall in systemic arterial pressure again occurred on positive pressure inflation (Fig. 15). In an another experiment, an inflation was begun with

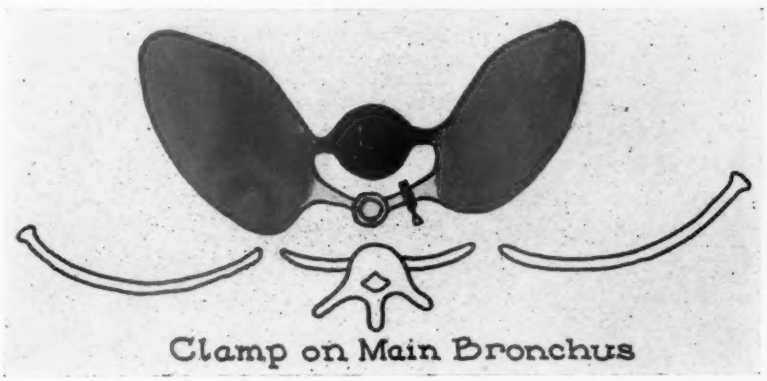

Fig. 11.—The main bronchus of one lung is clamped so that during pulmonary inflation a free pulmonary circulation would be available through the undistended lung.

both the pulmonary artery and main bronchus to one lung obstructed. This produced the usual fall in systemic arterial blood pressure, but when the pulmonary artery clamp only was released, the systemic blood pressure returned to preinflation levels although the inflation was still being maintained (Fig. 16). These experiments demonstrated that when all possibility of tamponade had been removed, positive pressure pulmonary inflation was capable of producing systemic circulatory depression by obstruction of the pulmonary vascular bed.

DISCUSSION

The circulatory changes produced by increased intrapulmonary pressure have been the subject of many investigations. The conclusions reached have been varied and depend largely on the nature of the experimental preparation and the degree of positive pressure used. Previous studies fall into three main groups: those concerned with low pressures applied for long periods in conscious, healthy subjects; those concerned with low pressures over long periods

A. B.

Fig. 12.—In Experiment A both lungs were inflated at 3 cm. Hg pressure as shown by signal. A fall in femoral artery pressure and a rise in pulmonary artery pressure were produced. Experiment B shows the result of a similar inflation in which one main bronchus was occluded, thus providing a free pulmonary circulation through the undistended lung. The femoral artery pressure is little affected and there is less rise in pulmonary artery pressure.

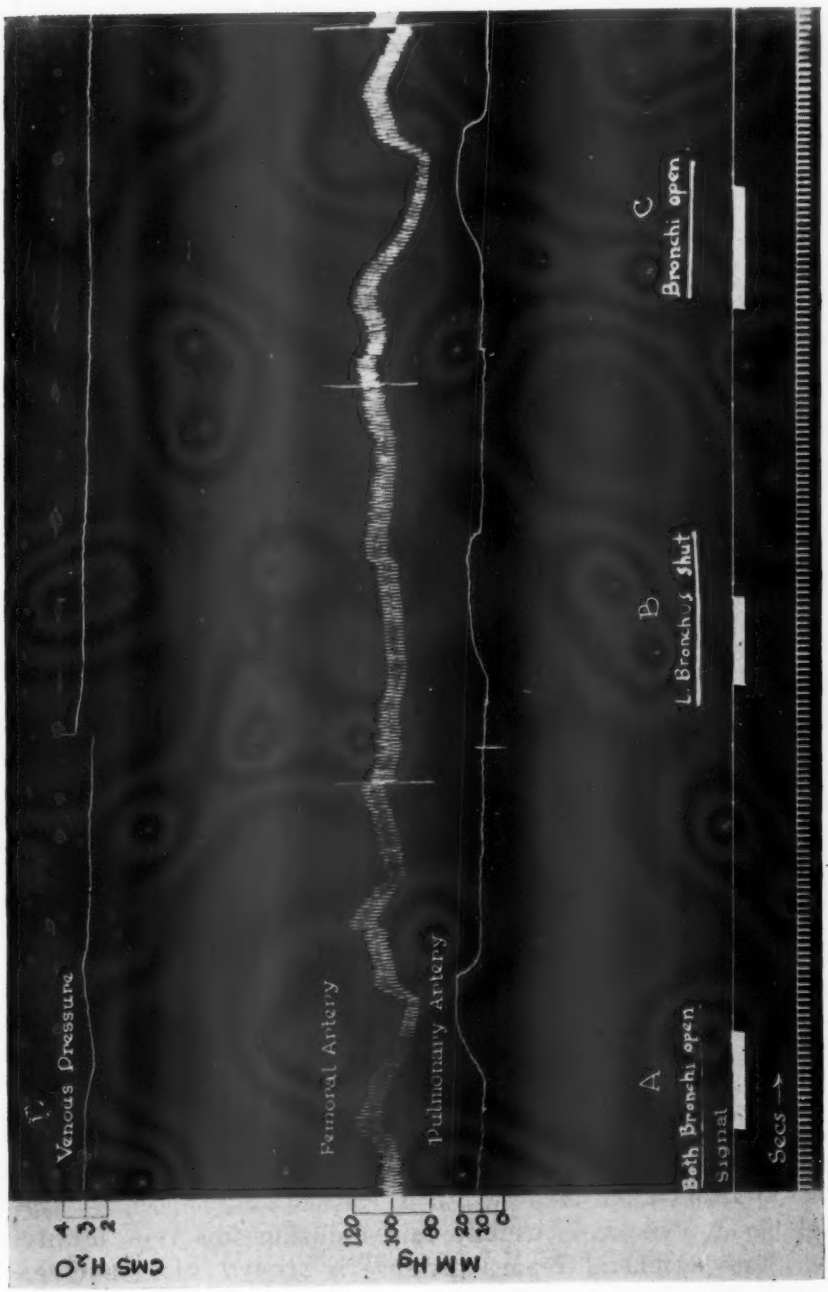

Fig. 13.—Results of 3 inflations as indicated by the signals. In Experiments A and C, both lungs were inflated and a fall in femoral artery pressure was produced. In Experiment B, one main bronchus was clamped and there was little alteration of femoral artery pressure during inflation. The external jugular vein pressure indicates that tamponade was not a factor in these experiments.

in anesthetized subjects; those in which relatively high pressures have been used for brief periods in unconscious subjects.

Group I.—Workers in the field of aviation medicine have comprehensively studied the effect of small increases in intrapulmonary pressure continued for long periods in the conscious subject. Otis, Rahn, Brontman, Mullins, and Fenn[19] concluded that breathing against a positive pulmonary pressure which is elevated during inspiration only decreases the cardiac output to 85 per cent of normal, while Cournand, Motley, and associates[20] demonstrated that if a mean mask pressure of 5.7 mm. of mercury is applied during inspiration only and if expiration takes place at atmospheric pressure and occupies as long a

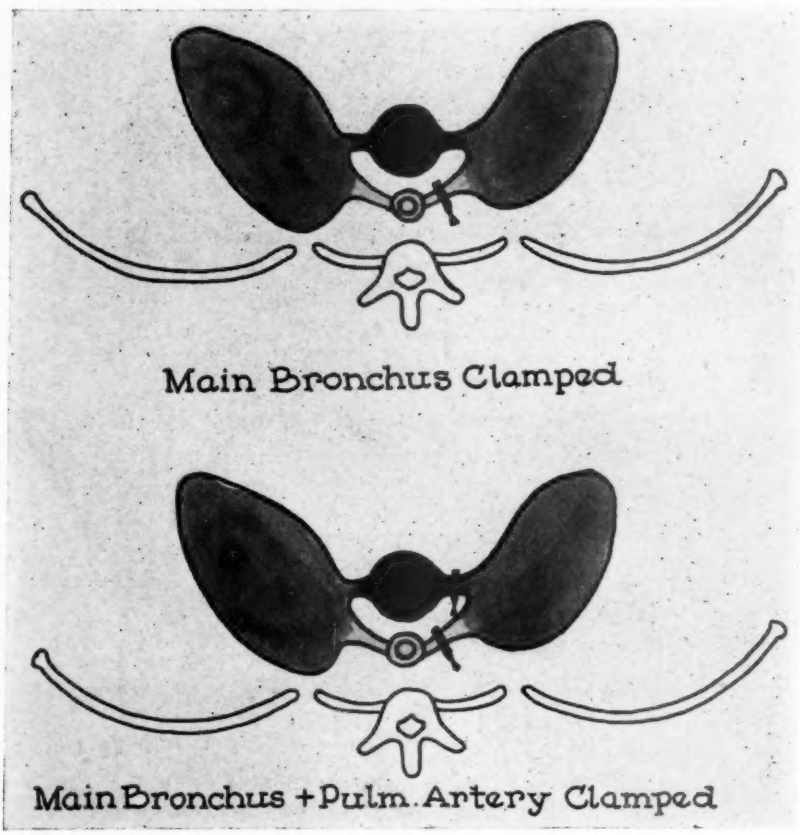

Fig. 14.—Preparation shown in Fig. 11 modified by the addition of a clamp to the pulmonary artery of the undistended lung.

period of time as inspiration, then no fall in cardiac output occurs. The systemic arterial blood pressure is usually raised during this type of pressure breathing, and the peripheral venous pressure is always raised and may in time lead to an accumulation of fluid in the tissue spaces of the limbs. Henry and associates[21] have estimated that pressure breathing for 30 minutes at 30 mm. of mercury leads in the average subject to a calculated loss into the tissues of 4 per cent of the blood volume. In the conscious subject, if the inflation pressure exceeds a certain level, then syncope with rapid decline in arterial blood pressure

occurs, and Drury and co-workers[22] stated that continuous pressure breathing of 16 mm. of mercury can be tolerated by a healthy, conscious man, but that at pressures of 25 to 40 mm. of mercury circulatory collapse and fainting become frequent.

Group II.—Several workers have studied the effects of low positive pressure pulmonary inflation in the anesthetized animal. Humphreys and associates[16] demonstrated that a reduction in cardiac output occurs under these conditions, and Carr and Essex,[23] and Beecher and associates[24] showed that if the animal's clinical state was poor, the mortality from pressure breathing was high. It was considered that once the organism was unable to maintain a high peripheral

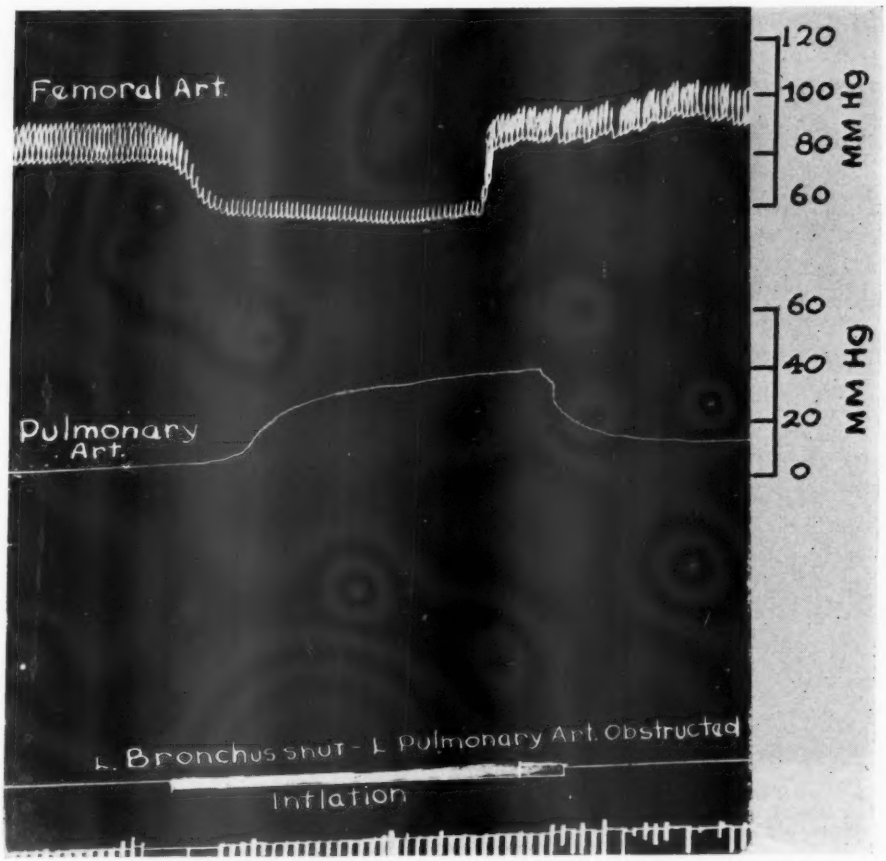

Fig. 15.—Pulmonary inflation with both main bronchus and pulmonary artery clamped as shown in Fig. 14. The free pulmonary circulation through the distended lung is no longer available and a fall in femoral artery pressure is produced during inflation.

venous pressure owing to decreased blood volume or loss of peripheral venous tone, then cardiac filling and hence cardiac output became inadequate to support life. With the low pressures used in these studies, arterial systemic blood pressure was lowered only slightly, the reduction in cardiac output presumably being compensated for by peripheral vasoconstriction until the compensatory mechanism failed when the animal became shocked or was bled.

In the majority of these investigations the emphasis has been on the obstruction of the venous return to the heart by the high intrathoracic pressure, while the pulmonary circulation per se received scant attention.

Group III.—In this group, the effect of relatively high intrapulmonary pressure (15 to 50 mm. of mercury) for short periods was studied and most of the investigative work described in this paper falls into this category. The drop in cardiac output is more pronounced under these conditions and cannot be fully compensated for by peripheral vasoconstriction. The resultant depression in arterial blood pressure can therefore be used as an approximate indicator of the degree of circulatory depression. Studies on the Valsalva maneuver are also included in this section, although, of course, the rise in intrapulmonary pressure is self-produced by a conscious subject.

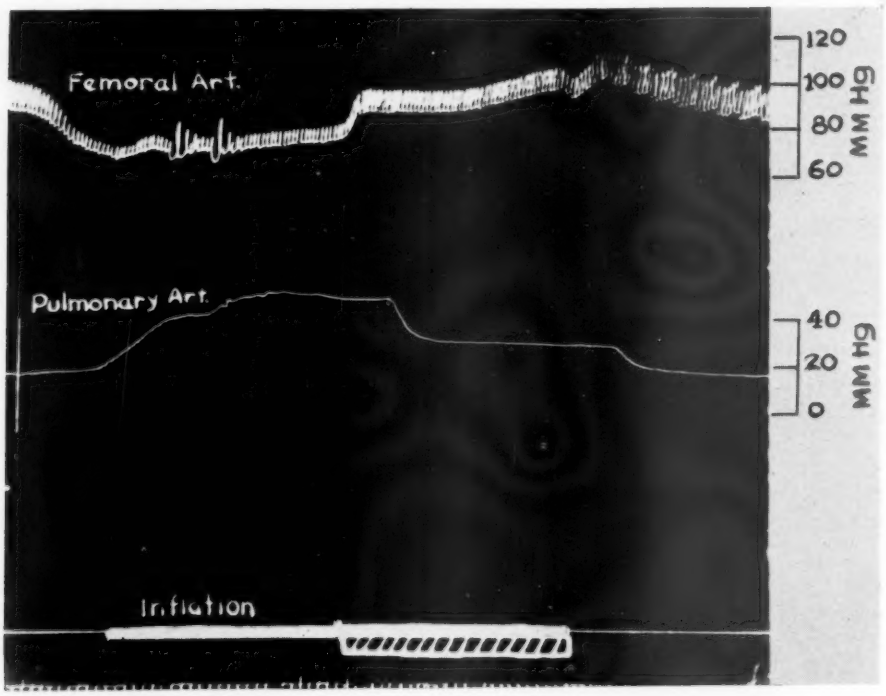

Fig. 16.—Pulmonary inflation at 3 cm. Hg indicated by solid white signal line. Experiment was begun with one main bronchus and pulmonary artery clamped (Fig. 14). At lower cross-hatched signal, the clamp on the pulmonary artery only was removed, thus releasing the pulmonary circulation of the undistended lung. At this point, the pulmonary artery pressure fell and the femoral artery pressure rose to a normal level although inflation was still being maintained.

The circulatory effects of these short periods of high pressure inflation of the lungs have been the subject of several investigations, and of the various theories on the mechanism of the reduction in systemic arterial pressure, all but one have been championed at one time or another. General agreement on the exclusion of an autonomic reflex pathway seems to have been reached, however, and it has been found that denervation of possible reflex pathways did not significantly alter the circulatory response to pulmonary inflation.[9, 11-13, 25] Cur-

rently, the tamponade factor is held as being the most important and has received investigative support, although in most of these studies the role of the pulmonary vascular bed has not been investigated.[16, 25]

Conversely, other workers in this field have concluded that the responsible factor is the obstruction of the pulmonary circulation by the high pressure, preventing adequate filling of the left ventricle.[11-13] However, in these experiments, the possibility of tamponade was either not considered or dismissed without adequate investigation.

In the experiments reported in this paper it has been shown that, with tamponade excluded, circulatory depression can still occur, and that the role of the pulmonary circulation may be important in this respect when high pulmonary inflation pressures are used.

Recently, some interesting observations on a patient suffering with tussive syncope have been recorded.[26] It has been shown that if this subject performed the Valsalva maneuver, expiring forcibly against a resistance of 40 mm. of mercury, syncope resulted with a fall in systemic arterial blood pressure to 40 mm. of mercury and a rise in right ventricular diastolic pressure as high as 75 mm. of mercury. This indicated not only that an obstruction of the pulmonary circulation was present, but also that an adequate venous return to the right heart was being maintained to support the high right intraventricular pressure.

We feel that insufficient attention has been paid to the obstructive effect on the pulmonary circulation by pressure inflation of the lungs and we wish to emphasize that any rise in intra-alveolar pressure acts directly on the pulmonary capillary bed and will produce a direct strain on the right ventricle. In addition, the decline in left ventricular pressure and the rise in right ventricular pressure during acute pulmonary inflation tends to reverse the normal gradient of the coronary circulation and might lead to myocardial embarrassment. This may afford an explanation for certain instances of circulatory collapse or cardiac arrest occurring during operations upon the heart or great vessels. The heart and circulatory system already heavily burdened by congenital or acquired disease may not tolerate slight increases in peripheral resistance in the pulmonary circulation.

CONCLUSIONS

1. In the anesthetized animal, short duration positive pressure pulmonary inflation produced air embolism, mediastinal emphysema, and circulatory depression at 10 cm., 7 cm. and 1.5 cm. of mercury pressure, respectively.

2. The rise in venous pressure caused by brief periods of pulmonary inflation is not an accurate indicator of the systemic arterial pressure response.

3. Obstruction in the pulmonary vascular bed is an additional factor to tamponade in the production of circulatory depression during pressure inflation of the lungs.

We wish to thank Sir James Paterson Ross, Director of The Surgical Professorial Unit, St. Bartholomew's Hospital, London, and Professor E. C. Amorosa of the Royal Veterinary College, London, for their guidance and encouragement, and Mr. N. C. Comben, M.R.C.V.S., and Miss D. Gay for their able assistance during this study.

REFERENCES

1. Crafoord, Clarence: Pulmonary Ventilation and Anesthesia in Major Chest Surgery, J. Thoracic Surg. **9**: 237, 1940.
2. Mautz, F. R.: A Mechanism for Artificial Pulmonary Ventilation in the Operating Room, J. Thoracic Surg. **16**: 50, 1947.
3. Polak, B., and Adams, H.: Traumatic Air Embolism in Submarine Escape Training, U. S. Nav. M. Bull. **30**: 165, 1932.
4. Van Allen, C. M., Hrdina, L. S., and Clark, J.: Air Embolism From the Pulmonary Vein, Arch. Surg. **19**: 567, 1929.
5. Joannides, M.: Insufflation of Compressed Air in the Treatment for Pneumonia, Arch. Int. Med. **47**: 196, 1931.
6. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels From Alveoli to Mediastinum, Arch. Int. Med. **64**: 913, 1939.
7. Marcotte, R. J., Phillips, F. J., Adams, W. E., and Livingstone, H.: Differential Intrabronchial Pressures and Mediastinal Emphysema, J. Thoracic Surg. **9**: 346, 1940.
8. Macklin, M. T., and Macklin, C. C.: Malignant Interstitial Emphysema of the Lungs and Mediastinum as an Important Occult Complication in Many Respiratory Diseases and Other Conditions; An Interpretation of the Clinical Literature in the Light of Laboratory Experiment, Medicine **23**: 281, 1944.
9. Sarnoff, S. J., Hardenbergh, E., and Whittenberger, J. L.: Mechanism of the Arterial Pressure Response to the Valsalva Test; The Basis for its Use as an Indicator of the Intactness of the Sympathetic Outflow, Am. J. Physiol. **154**: 316, 1948.
10. Wilkins, R. W., and Culbertson, J. W.: Effect of Surgical Sympathectomy Upon Certain Vasopressor Responses in Hypertensive Patients, Tr. A. Am. Physicians **60**: 195, 1947.
11. Johnson, C. A., and Luckhardt, A. B.: The Effect of Raised Intrapulmonic Pressure Upon the Knee Jerk, Arterial Blood Pressure and State of Unconsciousness, Am. J. Physiol. **83**: 642, 1928.
12. Sharpey-Schafer, E., and Bain, W. A.: The Effects of Changes in Intrapulmonary Air Pressure on the Pulmonary and Aortic Circulation of the Dog, Quart. J. Exper. Physiol. **22**: 101, 1932.
13. Chillingworth, F. P., and Hopkins, R.: Physiologic Changes Produced by Variations in Lung Distention. II. Efficiency of the Pulmonary Circulation in Overcoming Obstruction, Am. J. Physiol. **51**: 289, 1920.
14. Humphreys, G. H., Moore, R. L., and Barkley, H.: Studies of the Jugular, Carotid and Pulmonary Pressures of Anesthetized Dogs During Positive Inflation of the Lungs, J. Thoracic Surg. **8**: 553, 1939.
15. Humphreys, G. H., Moore, R. L., and Barkley, H.: Studies of the Jugular Pressures of Anesthetized Dogs During Positive Inflation of the Lungs Before and After Pneumonectomy, SURGERY **10**: 21, 1941.
16. Humphreys, G. H., Moore, R. L., Maier, H. H., and Apgar, V.: Studies of the Cardiac Output of Anesthetized Dogs During Continuous and Intermittent Inflation of the Lungs, J. Thoracic Surg. **7**: 438, 1938.
17. Barach, A. L., Eckman, M., Ginsberg, E., Rumsey, C. C., Jr., Kor, I., Eckman, I., and Besson, G.: Studies on Positive Pressure Respiration J. Aviation Med. **17**: 290, 1946.
18. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**: 764, 1923.
19. Otis, A. B., Rahn, H., Brontman, M., Mullins, L. J., and Fenn, W. O.: Changes in Cardiac Output Due to Respiration, J. Clin. Investigation **25**: 413, 1946.
20. Cournand, A., Motley, H. L., Werko, L., and Richards, D. W.: Physiological Studies of the Effects of Intermittent Positive Pressure Breathing on Cardiac Output in Man, Am. J. Physiol. **152**: 162, 1948.
21. Henry, J. P., Hendrikson, E., Movitt, E., and Meehan, J. P.: Estimations of the Decrease in Effective Blood Volume When Pressure Breathing at Sea Level, J. Clin. Investigation **27**: 700, 1948.
22. Drury, D. R., Henry, J. P., and Goodman, J.: The Effects of Continuous Pressure Breathing on Kidney Function, J. Clin. Investigation **26**: 945, 1949.
23. Carr, D. T., and Essex, H. E.: Certain Effects of Positive Pressure Respiration on the Circulatory and Respiratory Systems, Am. Heart J. **31**: 53, 1946.
24. Beecher, H. K., Bennett, H. S., and Bassett, D. L.: Circulatory Effects of Increased Pressure in the Airway, Anesthesiology **4**: 612, 1943.
25. Dawson, P. M., and Hodges, P. C.: Cardiovascular Reaction in the Valsalva Experiment and in Lifting With a Note on Parturition, Am. J. Physiol. **50**: 481, 1920.
26. McCann, W. S., Bruce, R. A., Lovejoy, F. W., Jr., Yu, P. N. G., Peason, R., Emerson, E. B., Engel, G., and Kelly, J. J.: Tussive Syncope, Arch. Int. Med. **84**: 845, 1949.

DISCUSSION

DR. HERBERT C. MAIER.—This excellent work has important clinical and theoretical implications. It also indicates the inadvisability of a common clinical practice. I am referring to the custom of some surgeons to rely upon the use of high positive intratracheal pressure to force the remaining air out of the pleural space at the conclusion of an intrapleural operation, or when an opening inadvertently has been made into the pleura. When the pleura is widely open and the air has free egress from the pleural cavity, only a slightly positive pressure is necessary. It is undesirable, however, when a high intrathoracic pressure is produced in an attempt to force air out of a small opening. Moreover, considerable air may remain trapped within the pleura space with that technique. It is far more physiologic to aspirate the remaining air by means of a catheter and syringe.

At the present time it is obvious that one of our great problems is to lessen the undesirable circulatory effects of positive pressure while we try to avoid accumulations of carbon dioxide during transpleural operations. We have noted in some of our patients in whom we have studied the carbon dioxide content of the blood during operation that in attempting to correct the acidosis we have produced some drop in blood pressure which is undoubtedly due to the mechanism that has been so beautifully demonstrated by Dr. Taylor and Dr. Gerbode.

DR. GERARD TAYLOR (Closing).—I wish to thank Dr. Maier for his discussion and to say that we have measured arterial pressures in the operating room during thoracic procedures and have found that there can be a significant depression in the systemic arterial pressure when the anesthetist is re-inflating the collapsed lung.

THE ROLE OF PELVIC EVISCERATION IN SURGERY

EUGENE M. BRICKER, M.D., AND JOHN MODLIN, M.D., ST. LOUIS, MO.

(From the Department of Surgery, Washington University School of Medicine, St. Louis, Mo., and the Department of Surgery, Ellis Fischel State Cancer Hospital, Columbia, Mo.)

MOUNTING interest has been shown in recent months in the treatment of advanced pelvic cancer by means of pelvic evisceration, and it is apparent that initial enthusiasm may well outstrip objective evaluation of the true role of such surgery. There are certain aspects of the pelvic evisceration problem that should be considered as completely experimental. This applies particularly to the application of the operation to the treatment of recurrent carcinoma of the cervix. We would urge that this problem should be approached, not by the occasional surgeon, but only by those institutions equipped for investigative radical surgery and where a significant volume of cases may be expected to accumulate. Although our own experience is numerically inferior to that of others, we have been interested in the problem for some time and wish to present our current evaluation of this procedure.

It appears that the first successful cases of complete pelvic evisceration were performed by Appleby,[1] who in January, 1950, reported one seven-year, one five-year and two four and one-half year survivors. Carcinoma of the rectum in males accounted for all his cases. One of us (E. M. B.) had performed the procedure twice in 1940,[2] each case terminating in an operative fatality. Three other patients undergoing partial pelvic evisceration at that time survived for varying periods but died of recurrent disease or renal complications. Brunschwig[3] was the first to report the procedure, referring to cases done in 1946. It is to him that credit belongs for the intensification of interest that has recently developed. His application of the operation to patients with carcinoma of the cervix has added greatly to its potential importance since rectal carcinomas, for which such radical measures might be indicated, are only occasionally encountered by the individual surgeon. Recent accounts of pelvic evisceration reaching the literature include those of Brintnall and Flocks[4] and Parsons and Bell.[5]

MATERIAL

Our experience is based on thirty-two cases of pelvic evisceration performed for a variety of lesions by ourselves or by close colleagues. The over-all operative mortality, which includes cases done in 1940, is 34 per cent. If the figures are corrected to include only those operations performed since the war at Barnes Hospital and the Ellis Fischel State Cancer Hospital, the mortality drops to five deaths out of twenty-two cases, or 23 per cent. Brunschwig and Pierce,[6] recently reporting on their first 100 patients, indicated a mortality rate of 17 per cent for complete pelvic evisceration. With the more judicious selection of patients we believe that this initial operative risk will soon decline to a more acceptable figure of around 10 per cent.

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The procedure has been done by us on fifteen patients with postirradiation carcinoma of the cervix, carcinoma of the uterus, and carcinoma of the vagina in the past year. Five patients did not survive the operation; one has died subsequently of persistent carcinoma. All of the nine survivors have been relieved of pain and discomfort and have been given new hope of life. Six patients have recovered sufficiently to return to their household duties. Of the five patients who did not survive, three were preventable deaths; one should not have been operated upon at all because of her age of 73 years; the other two died in the operating room following poor technical management. These factors would seem to indicate that the operative mortality can be made more acceptable with time and experience. Two of the patients listed as operative deaths and a third who died more than a month following operation are considered not only to have received no benefit from the operative attempt, but their physical and mental distress were indeed aggravated.

LESIONS FOR WHICH PELVIC EVISCERATION MIGHT BE CONSIDERED

Carcinoma of the cervix and rectum have accounted for the majority of our patients, but we have also performed the procedure for lesions of the prostate, bladder, uterus, and vagina. Our opinions concerning the various lesions for which the procedure might be considered are now fairly well crystallized and are as follows:

Carcinoma of the Prostate.—The inherent behavior characteristics of prostate cancer would seem to rule out the possibility of permanent control by means of pelvic evisceration in the great majority of patients. These tumors exhibit metastases to bone in 30 to 70 per cent of various reported series and visceral metastases also occur in about 40 per cent of the fatal cases.[7] Lymph node metastases have been noted in 65 to 75 per cent of autopsied patients[7, 8] and such metastases may involve distant lymph node groups. It thus appears that the probability of distant metastases is sufficiently great in the patient with advanced cancer of the prostate to preclude consideration of permanent cure by means of pelvic evisceration. Also, effective means of palliation already exist in the form of orchiectomy, estrogenic hormone therapy, and transurethral resection. We have performed pelvic evisceration on only three patients with carcinoma of the prostate. These were done in 1940, one survivor dying at eighteen months of generalized bone metastases. We would not now consider carcinoma of the prostate in any stage as a suitable lesion for this operation.

Carcinoma of the Bladder.—The eventual role of pelvic evisceration in treatment of this type of cancer is difficult to evaluate at the present time. It is only in recent years that total cystectomy has been widely applied to the treatment of these lesions[9-13] and insufficient time has elapsed to determine curability by this method. Lymphatic drainage of the bladder is mainly to lymph nodes along the external iliac, epigastric, and common iliac vessels[14] and metastases to these nodes have been reported in approximately 30 per cent of patients coming to autopsy.[13, 15, 16] Distant metastases, however, add to the total percentage of patients who exhibit spread beyond the bladder and have been noted in approximately one-third of fatal cases.[7] This tendency to remote

metastases by means of the blood stream is apparently greater than in cancer of the cervix and the probability of such metastases is a deterrent to treatment by means of pelvic evisceration. Our experience with this lesion includes two patients with advanced disease operated upon in 1940. Although the procedure done at that time was a more limited one, it is significant that both patients exhibited short survival periods and that, at autopsy, cancer was found to be present in the pelvis of each. In a recent patient, operated upon because of unusual local lymphatic metastases, although the operation was grossly satisfactory as a cancer resection, such extensive lymphatic, venous, and perineural permeation has been shown that a short survival is expected. If a bladder lesion is so far advanced as to be unsuitable for total cystectomy and pelvic lymph node dissection as advocated by Leadbetter and Cooper,[13] it is doubtful if pelvic evisceration would appreciably add to the chance of cure.

Carcinoma of the Vagina.—Only one patient has been subjected to pelvic evisceration in our series; she had a huge untreated tumor of the posterior vaginal wall and with ulceration into the rectum. Because of the fistula and the size of the tumor, it was decided to treat the lesion by radical surgical extirpation rather than by irradiation therapy. This patient is a twelve-month survivor without evidence of recurrent disease. In general, primary carcinoma of the vagina should be considered in much the same light as carcinoma of the cervix, irradiation therapy being the primary treatment of choice. However, unusual features of this lesion, as in the case just cited, may favor pelvic evisceration as the primary treatment. Postirradiation recurrence or persistence of carcinoma of the vagina might possibly be considered as an indication for pelvic evisceration, depending on the size and location of the lesion.

Carcinoma of the Uterus.—Adenocarcinoma of the endometrium presents features which make it possible to consider selected cases for pelvic evisceration. Lymphatic spread occurs late in the course of this disease and, when present, most frequently involves lymph nodes that are removed by pelvic evisceration. The most generally accepted method of treatment of endometrial carcinoma is by surgical extirpation and/or irradiation. There is no reason why pelvic evisceration should not be applied in patients with more advanced endometrial cancer in which local extension precludes cure by conventional means. Another instance in which evisceration might be justifiable is that of recurrent endometrial carcinoma after inadequate surgery. In our series, there have been only two patients with endometrial carcinoma subjected to evisceration. It is surprising that more candidates with this lesion are not seen. There is nothing in the mode of spread or the behavior characteristics of this tumor that would contraindicate pelvic evisceration in properly selected cases.

Radionecrosis.—Radionecrosis with no demonstrable persistence of neoplasm is a not uncommon finding following irradiation for carcinoma of the cervix. Biopsy from the edges of sloughing postirradiation ulcers means nothing if negative. Therefore, it may become necessary to consider a patient as a candidate for pelvic evisceration without having demonstrated persistent tumor. The procedure is especially indicated if the slough has developed to the point of formation of vesicovaginal and/or rectovaginal fistulas with their distressing

symptoms. Even though persistent cancer may not be demonstrated, these patients are still doomed to a life of chronic invalidism and misery. Pelvic evisceration may result in satisfactory palliation in the patient with persistent cancer and radionecrosis, and in the patient with radionecrosis alone the result can be even more gratifying.

Carcinoma of the Rectum.—From the standpoint of behavior characteristics, there can be little argument that carcinoma of the rectum is suitable for pelvic evisceration. It is a well-known clinical fact that many carcinomas of the rectum and rectosigmoid colon may show extensive local involvement without any evidence of remote spread. If the urinary tract is involved, pelvic evisceration may be perfectly justifiable. Carcinoma of the rectum tends to spread by lymphatic metastases to the lymph nodes in the mesentery of the sigmoid colon and is less likely to spread to lymph nodes in the lateral aspect of the pelvis, thus the situation is ideal for wide surgical excision. The longest results of pelvic evisceration are reported in patients who had resections for rectal cancer.[1, 2] Although the number of cases of carcinoma of the rectum that may be found suitable for pelvic evisceration may be small, it is here that the procedure will have its most definite and incontrovertible indications.

Carcinoma of the Cervix.—It is in the treatment of postirradiation recurrent cancer of the cervix that pelvic evisceration has to date been most often applied and it is for this type of cancer that the operation will probably continue to be most often recommended in the future. At the present time, the proved value of irradiation methods in the primary treatment of cancer of the cervix cannot be disputed.[17, 18] The rate of cure by such methods is higher than in any other major form of cancer.[19] Nevertheless, approximately three out of five women who have this disease fail to have permanent control following irradiation, and since cancer of the cervix is the second most frequent type of cancer in women[20, 21] the number of patients who may be considered for further treatment by means of pelvic evisceration is appreciable.

Clinical studies of the behavior pattern of cancer of the cervix reveal that contrary to other types of cancer, death frequently occurs while the disease is still confined to the pelvis. In a series of sixty-five necropsies at Memorial Hospital in patients dying of cancer of the cervix, Brunschwig and Pierce[22] found that the disease was limited to the pelvis in 50 per cent of the patients and that uremia and infection were the cause of death in 66 per cent of the patients. Morris and Meigs,[23] in a recent article, stated that on the basis of clinical studies including x-ray and surgical procedures, local recurrence in the pelvis was seven times more frequent than distant metastases. It is evident that from the standpoint of the probability of distant metastases in the patient with postirradiation recurrent cancer of the cervix these lesions are undoubtedly favorable for treatment by pelvic evisceration.

In a recent survey[24] of forty-five patients admitted to the Ellis Fischel State Cancer Hospital with a history of previous inadequate surgical treatment for carcinoma of the cervix, only two patients, or 4 per cent, were alive and free of disease five years following irradiation management. From the data in

this admittedly small series, it would seem that consideration should be given to primary treatment by means of pelvic evisceration if, in the future, the morbidity and mortality of this procedure continues to be lowered. To date, however, we have not performed pelvic evisceration as the primary treatment in such patients.

It is unlikely that the radioresistance of any particular carcinoma of the cervix will prove to be an indication for pelvic evisceration as a primary means of treatment. Regato[19] denied the concept of the radioresistant epidermoid carcinoma of the cervix. Heyman and Belonoschkin,[25] while reporting instances of failure of response to irradiation, emphasize that these cases probably coincide with a more pronounced malignancy and that probably no method of treatment, including surgery, will be effective.

Our own experience with pelvic evisceration for recurrent carcinoma of the cervix is not great but has permitted us to formulate certain definite ideas which are enumerated below:

1. Observation of the lingering painful course of the patient with post-irradiation recurrence leads to the conclusion that any procedure is justified which even temporarily halts the usual chain of events and allows the individual to return to a comfortable existence with her family. This, pelvic evisceration can accomplish in selected patients. In considering this problem it is important to realize also that, although any effective palliation represents pure salvage, there is nevertheless a moral obligation to exercise the utmost care in selection of patients in order that the "aggravation rate" not be excessive. By "aggravation rate" we refer to that group of patients who not only fail to receive effective palliation but whose terminal days are made even more miserable by the operation.

2. If such a lesion is to be subjected to surgery the very nature of the situation demands that the resection be as wide as possible. We do not believe that the bladder or rectum can be retained safely in such patients. The operation is the last chance against recurrent disease. It is impossible for a wide resection for recurrent carcinoma of the cervix to be done without sacrificing all pelvic viscera. Thus, the choice of operative procedure is simplified.

3. Since spread from carcinoma of the cervix is predominantly lateral, the lateral plane of dissection must be as wide as possible. We establish this plane lateral to the hypogastric artery and internal iliac vein. We feel that this technique has facilitated the satisfactory removal of some lesions which have presented evidence of rather far-advanced fixation to the lateral pelvis on physical examination.

4. Regarding contraindications to pelvic evisceration, those relating to the general condition of the patient are perhaps the most definite. We have established 60 years as the age beyond which we are very careful about applying the procedure. Distant metastases, of course, would make this procedure inadvisable. Very severe pain over the sciatic distribution associated with palpable tumor on that side is suggestive but not pathognomonic of inoperability. At laparotomy, liver metastases or metastases to the para-aortic lymph nodes will

most often be the finding conclusively proving the lesion to be inoperable. We are not yet sure what to consider a contraindication to operation from the standpoint of findings on manual examination of the pelvis. The proper evaluation of these local findings presents one of the most important aspects of this whole problem since it pertains to the recognition of early recurrence as well as to the determination of operability of the advanced lesion. It has been our practice to explore patients surgically regardless of the extent of findings on vaginal and rectal examination. In cases that have appeared to be of borderline operability, surgical exploration has been very helpful. The question is usually answered by the lesion being found to be much less advanced than anticipated or by the demonstration of definite spread beyond the limits of resection, classifying the lesion as obviously inoperable. Perhaps the two most frequent findings on physical examination of the local lesion that pertain to resectability are fixation of the vaginal vault and the cervix in the arch of the symphysis, and thickening and fixation of the uterosacral ligaments and parametria. Immobility of the vaginal vault, cervix, and uterus in the arch of the symphysis are considered of little importance as a physical finding indicating inoperability since it takes very little inflammation or invasion to limit mobility in this area. Thickening and immobility of the parametria and uterosacral ligaments are difficult to interpret since they may be entirely due to irradiation or inflammation and accurate evaluation of these local findings will have to await studies correlating them with the pathologic findings and the postoperative course.

5. Finally, if satisfactory palliation has been achieved in advanced cases of recurrent postirradiation carcinoma of the cervix, it is logical to presume that even more can be done if these operations are applied to the disease in an earlier stage. At the present time, our efforts are beng directed toward the early recognition of postirradiation recurrence.

BLADDER SUBSTITUTION

The method of bladder substition is a corollary of great importance but one which will be given only passing acknowledgment in this presentation. Our aim has been to discuss the therapeutic role of the resection procedure itself, not to debate the merits of the various reconstructive procedures which may be associated with it. We solve the problem of bladder substitution by transplanting the ureters to an isolated segment of terminal ileum which empties into a Rutzen bag on the right side of the abdomen.[26] We have found this procedure to be an eminently satisfactory solution to the problem. We do not use a "wet" colostomy, that is, drain the urine and feces through a common opening. Only time will determine whether or not the isolated intestinal segment will exhibit any real advantages over other methods of bladder substitution. For the purpose of this presentation it is enough to state that this phase of the problem is at present solved to our satisfaction by this method.

TECHNICAL PROCEDURE

Work-up and Evaluation of Patient.—Included in the obviously necessary studies are a detailed search for remote metastases and x-ray studies of the kid-

neys and ureters. Cystoscopic studies are made routinely only on patients with advanced rectal carcinomas in which the bladder is not sacrificed unless direct invasion of the trigonal area is demonstrated.

Preparation of Patient.—The general preparation does not differ from that for any other extensive operative procedure. Sulfasuxadine is used to prepare the colon and, in the absence of obstruction, castor oil is given twenty-four hours before operation and the patient is placed on a liquid diet. The castor oil preparation we have found to be so satisfactory as to completely outweigh all the physiologic and pharmacologic objections to its use.

Patients with carcinoma of the rectum for whom pelvic evisceration is contemplated have ureteral catheters inserted just before the operation after anesthesia.

Anesthesia.—The preference at the Barnes Hospital in St. Louis is for endotracheal gas-oxygen-ether after Pentothal induction and with the use of curare to supplement relaxation. At the Ellis Fischel State Cancer Hospital the anesthetic of choice for some time has been continuous spinal with enough Pentothal to keep the patient in a drowsy state. Suffice it to say that either type of anesthesia is ideally suited to these long procedures and need only be expertly administered. It is no time, during procedures of this nature, for shock to be precipitated or contributed to by a poorly administered anesthetic.

Local Preparation.—Before preparation a final vaginal and rectal examination is done by the surgeon to check on the mobility, direction of extension, and points of attachment of the lesion. The anus is closed tightly with a heavy silk suture and the entire vulva, perineum, and inner surface of the thighs down to the knees are prepared with a soap containing G-11. If there is an ulcerated vaginal or cervical lesion, dry gauze is packed into the vagina after the preparation in order to prevent seepage. A sterile sheet is placed under the patient, the foot of the table is elevated and the legs are then taken out of stirrups and the stirrups removed. The patient is left low on the table for the entire operation. This greatly facilitates the subsequent elevation of the legs into the stirrups and the placing of the patient in the lithotomy position for the perineal dissection. The same soap preparation is used for the entire abdomen and for the anterior surface of the thighs.

Procedure.—Before drapes are applied, scratches are made on the abdomen to mark the sites of the subsequent colostomy and ileostomy (Fig. 1). A long midline incision is made and carried completely down to the pubic symphysis. A careful search is made for remote metastases, particular attention being paid to the liver and to the para-aortic lymph nodes. Exploration of the pelvis itself is aimed at determining the presence or absence of regional metastases, the resectability of metastatic involvement, and the resectability of the primary lesion itself with its area of direct extension. This latter point may be difficult to determine and actually may not be determined until late in the progress of the resection itself. However, a great effort should be made at this time to determine the course that may be expected to result in the most benefit to the patient. If the tumor cannot be circumscribed without cutting through gross cancer, we do not feel that benefit can accrue to the patient by resection. It

may be impossible to determine this factor without proceeding with the operation. In all cases with which we have proceeded thus far, we have not yet done one in which we felt we had committed a gross error. Aside from very extensive metastatic involvement of the iliac and hypogastric lymph nodes, the factor that is most likely to make a given case locally nonresectable is lateral extension of the primary tumor. Unfortunately, lateral extension of tumor may be difficult or impossible to differentiate from radiation fibrosis of the uterosacral ligament and parametria. In no case yet have we let lateral extension and fixa-

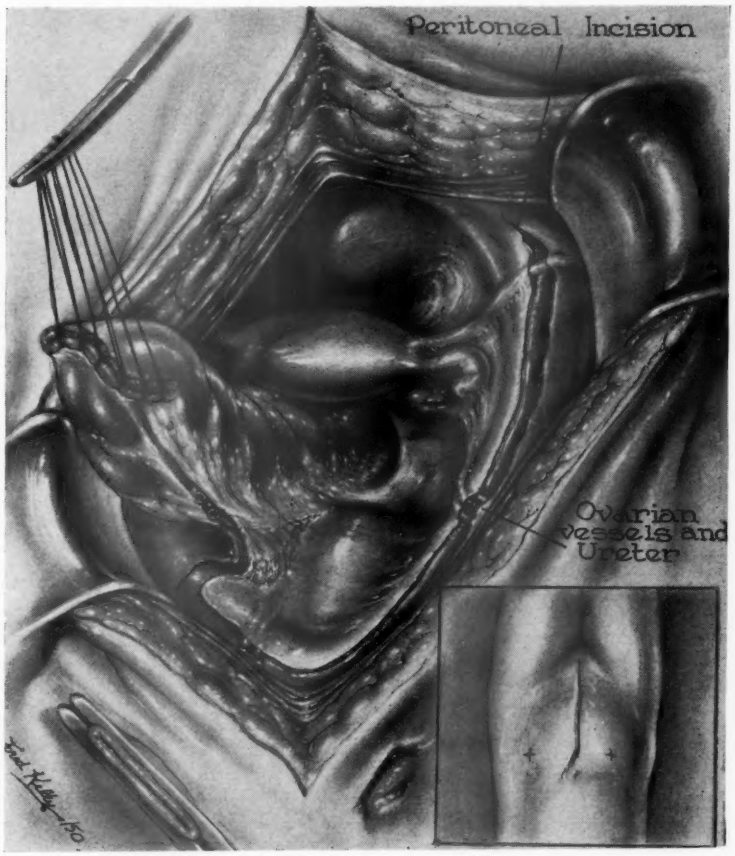

Fig. 1.—The sites for the subsequent ileostomy and colostomy are marked on the abdomen prior to the application of drapes. As soon as the lesion is considered operable the sigmoid colon and its mesentery are sectioned. The peritoneum is incised from the bifurcation of the aorta to the inguinal ligament, and the incision is then curved medially over the symphysis pubis.

tion alone be a deterrent to resection. Regional lymph node involvement is not a contraindication to resection as long as it is not associated with extensive direct lymphatic permeation by cancer and as long as there is no detectable involvement of the para-aortic lymph nodes. Attachment of metastatic lymph nodes to adjacent veins need not be a positive contraindication to resection.

As soon as it is decided that a resection will be done the sigmoid colon is sectioned, the proximal end is brought out through the accessory incision at the

predetermined spot in the left lower quadrant, and the distal end of the cut colon is closed with an inverting catgut suture. The lateral lumbar gutter is very carefully closed at this point. Theoretical objections to sectioning the colon at this period in the procedure because of possible contamination of the subsequent operative field are disregarded in favor of the practical advantage of having the colon freely maneuverable during the subsequent stages of the operation. The mesentery of the sigmoid colon is sectioned down to the superior hemorrhoidal vessels which are clamped, cut, and ligated at the level of the bifurcation of the aorta. The dissection is then carried over the promontory of the sacrum and the rectum is freed from the curve of the sacrum by anterior retraction and sharp dissection.

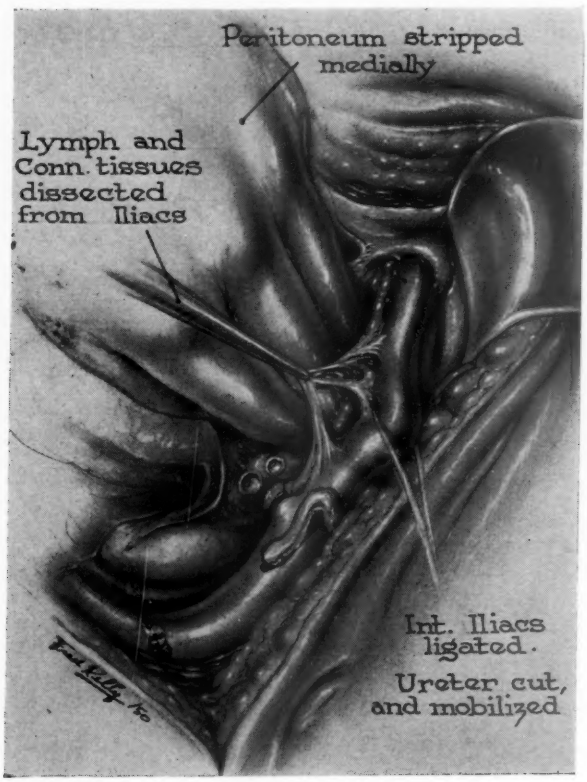
Peritoneum stripped medially
Lymph and Conn. tissues dissected from Iliacs
Int. Iliacs ligated.
Ureter cut, and mobilized

Fig. 2.—The lymph node dissection is started along the entire length of the iliac artery and all connective tissue and included lymph nodes are dissected in an inferior and medial direction. The ureter is sectioned just below the level of its crossing of the artery, the ovarian vessels are sectioned, and the origins of the hypogastric artery and internal iliac vein are carefully dissected out and these structures are ligated and sectioned.

The peritoneum is then incised from the bifurcation of the aorta along each iliac artery to the femoral canal (Fig. 1). The ovarian vessels are clamped, cut, and ligated at this level. The ureters are picked up and dissected for a distance of 3 or 4 cm. below the level at which they cross the iliac arteries and are here sectioned. If the ureters are not dilated a ligature is placed around the proximal cut end in order that it may dilate slightly in the time remaining before ureteral anastomosis is to be done. Slight dilatation of the ureter will

facilitate the anastomosis. The peritoneal incisions are then carried from the region of the femoral ring medially over the lower portion of the anterior abdominal wall to meet over the symphysis pubis. The bladder is very easily and quickly separated from the symphysis and this separation is carried laterally to the region of the femoral ring.

All attention is then directed to dissecting one side. As a rule, the side which is anticipated to present the least technical difficulties is done first. A complete dissection of the lymph nodes, connective tissue, and fat is done, starting along the entire length of the common and external iliac arteries and

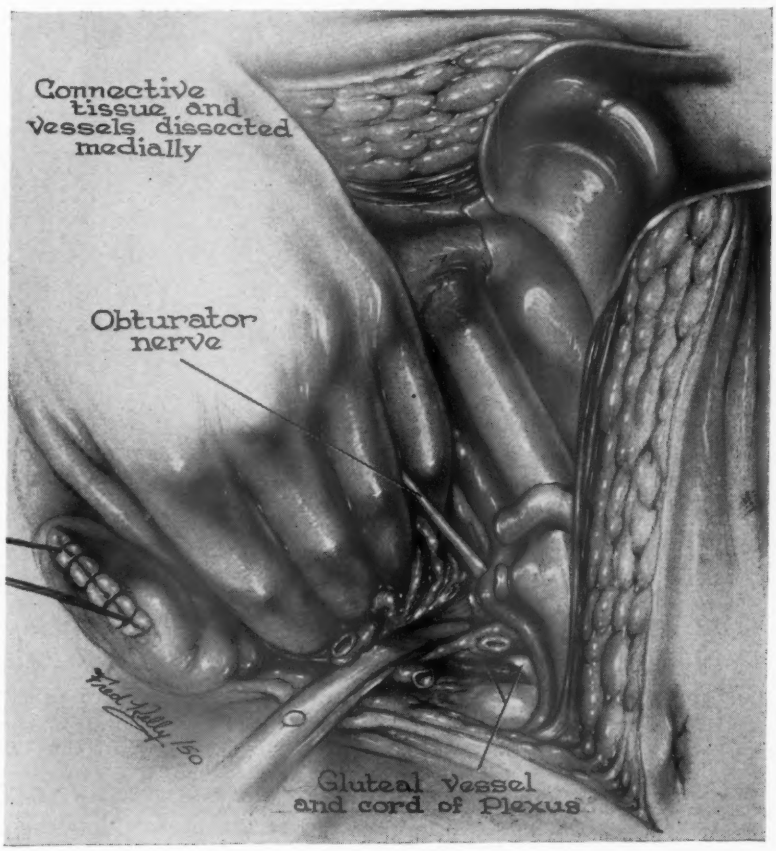

Fig. 3.—The dissection is carried into the obturator fossa, which is completely denuded of all connective tissue, fat, and lymph nodes. The obturator nerve is dissected in those cases without massive involvement of this area by metastatic disease. The nerve is sacrificed if it is felt its sacrifice will facilitate the lymph node dissection. The gluteal vessels are very carefully isolated, ligated, and cut as they are encountered. The superior cord of the sacral plexus comes into view after ligation and sectioning of the superior gluteal vessels.

descending on to the iliac vein (Fig. 2). The sheath of the iliac vein is removed and the obturator fossa beneath the vein and artery is emptied of all lymphatics and connective tissue until the obturator nerve is exposed throughout its length. The obturator vessels are carefully sectioned at their point of exit from the pelvis. It is very important that these vessels not be torn since they may retract into the obturator foramen and be very difficult to control. Attention is then

turned to the hypogastric artery and internal iliac vein. These structures are carefully isolated, ligated, and cut at their junctions with the common iliac vessels. The distal segments of these vessels are retracted medially and the dissection is carried in an inferior direction. As the gluteal branches are encountered, they are carefully ligated and cut until the superior cord of the sacral plexus comes into view (Fig. 3). The dissection is continued in this manner, the branches of the hypogastric artery and internal iliac vein being sectioned as they are encountered making their exit from the pelvis into the gluteal region. It is possible to accomplish this part of the dissection in a bloodless manner.

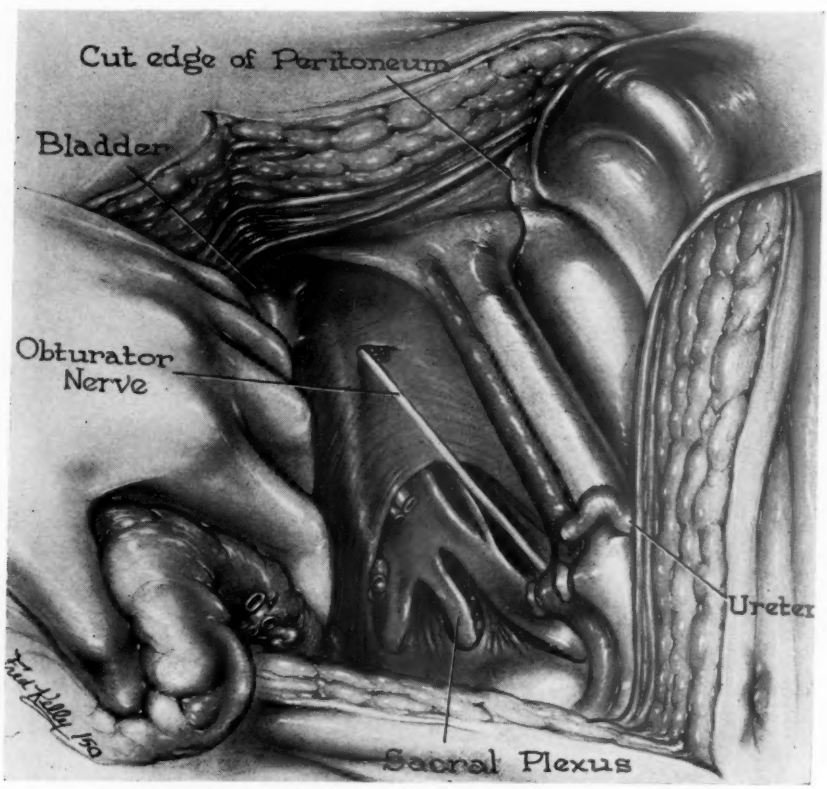

Fig. 4.—Completed dissection on one side, the sacral plexus and sciatic nerve are clearly visualized with the stumps of the gluteal vessels which have been ligated and cut. The hypogartric artery and internal iliac vein have been retracted medially, and the entire utero-sacral ligament has been freed from its lateral pelvic attachments. The dissection has been carried down to the pelvic diaphragm. The same dissection is then done on the opposite side.

At its termination, the complete lateral attachments of the cardinal ligaments and the parametria are freed from the lateral pelvic wall and the sacral plexus and sciatic nerve have been cleanly dissected into view (Fig. 4). In patients in whom irradiation has not been given to the pelvis and in whom there has not been a marked inflammatory element, this part of the procedure can be done as meticulously and as cleanly as an axillary dissection. In patients in whom there has been fibrosis and scarring from irradiation and infection, there are varying degrees of difficulty. Great care must be exercised not to injure the sacral plexus. This can very easily be done if there is hemorrhage from one of

the gluteal branches followed by the indiscriminate application of clamps. At the termination of this lateral dissection, the entire specimen, including the bladder, vagina, cervix, uterus, and rectum, is completely free from the lateral pelvic wall from the midline of the sacrum to the symphysis pubis and extending down to the levator sling. The same procedure is then accomplished on the other side. In order to prevent uncontrolled hemorrhage, the gluteal vessels are dissected free, ligated, and cut singly to keep the field free of instruments. Hemorrhage from the specimen side can be controlled easily by the retracting hand. Lateral hemorrhage must be carefully isolated and controlled without

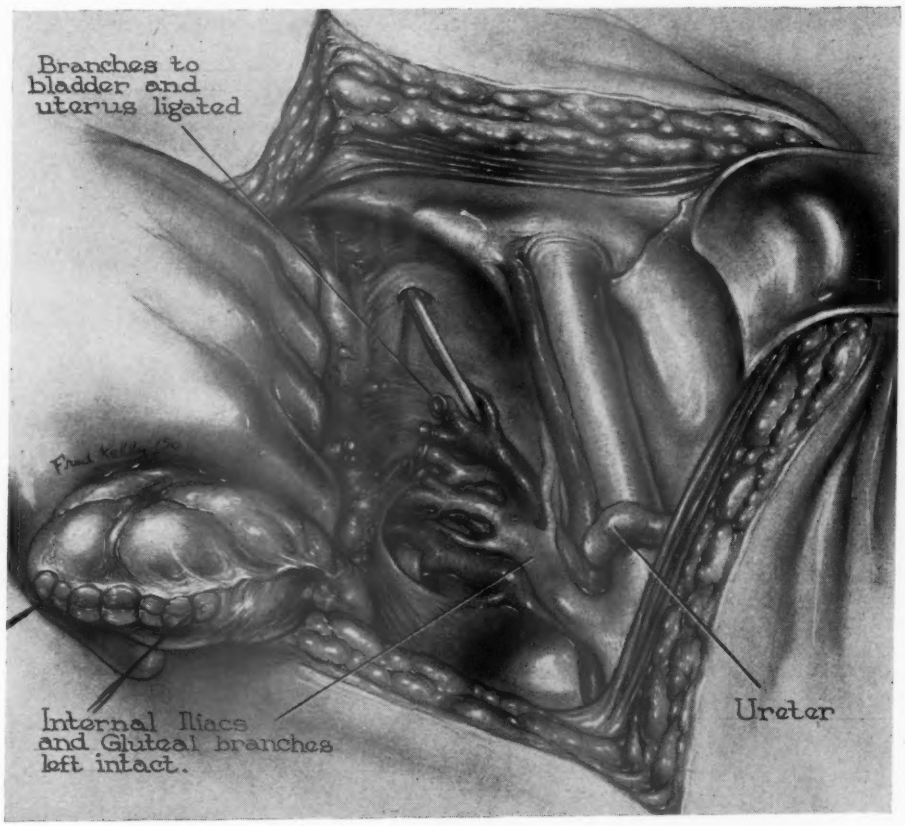

Fig. 5.—This figure illustrates the procedure as done for carcinoma of the rectum; the hypogastric and internal iliac veins are left in the pelvis, the specimen being freed by ligation of the uterine, vesical, and other terminal branches of these major blood vessels.

injury to the sacral plexus. Occasionally a large venous sinus will have to be controlled by a running transfixing suture which again must not involve the sacral plexus. It is imperative that long instruments and long suture materials be used for this dissection. After completing the dissection of the second side the specimen is ready for deliverance after the levator sling is sectioned from below.

Before starting the perineal portion of the dissection the ureters are anastomosed to an isolated segment of distal ileum. The continuity of ileum is reestablished by end-to-end anastomosis. This procedure is described elsewhere[26]

and will not be discussed in detail here. An end-to-side anastomosis, mucosa-to mucosa, of ureter to isolated segment of terminal ileum is done, and the distal end of this segment is brought out through the previously located accessory incision in the right lower quadrant. This method of disposing of the ureters can be accomplished in sixty to seventy-five minutes. It is done at wound level without undue retraction and without additional abdominal dissection.

Upon completion of the bladder substitution procedure the sheets over the patient's legs are removed and the legs are elevated and placed in stirrups.

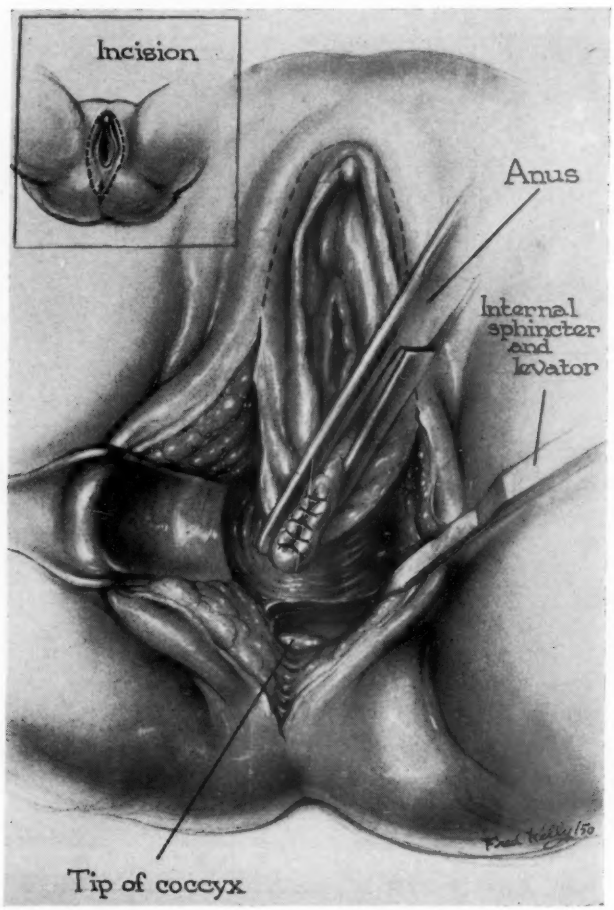

Fig. 6.—The perineal portion of the operation is accomplished in a manner similar to that of abdominoperineal resection of the rectum with the exception that the anterior viscera of the pelvis are included. The labia minora and clitoris are circumscribed by the incision. The pelvic diaphragm is sectioned as far laterally as possible.

The foot of the table is dropped and appropriate drapes are applied to the legs and perineum. With the perineum and the vagina already prepared and the anus closed, this maneuver can be accomplished in two to three minutes without moving the patient except to change the position of the legs. The abdominal wound is left open and covered with moist gauze.

An incision is made around the anus and including the labia minora and clitoris (Fig. 6). In two cases in which the clitoris was left it became edematous

and sensitive and was a discomfort to the patient. The posterior part of the dissection is done as the usual abdominoperineal rectal resection is accomplished. The fascia propria is cut and the levator muscles are sectioned widely at their attachment to the lateral pelvic fascia. The clitoris and labia minora are dissected down under the arch of the symphysis. The anterior pelvic diaphragm is sectioned along its lateral attachments and the entire specimen is removed. If the abdominal portion of the dissection has been carried to its completion, the perineal dissection can be done in 10 to 15 minutes with the greatest of ease.

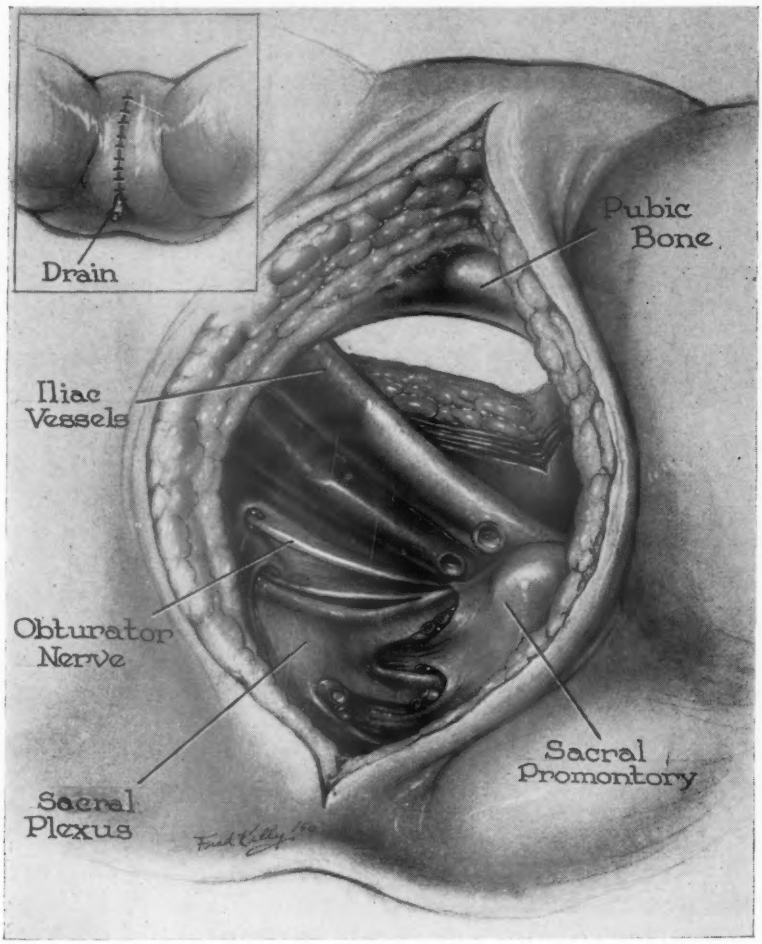

Fig. 7.—A view looking obliquely into the pelvis after the specimen has been delivered. Obviously, no attempt can be made to reform a peritoneal floor for the pelvis. The perineal opening is closed by layers of interrupted, nonabsorbable suture material closing the subcutaneous fat and skin. A drain is brought out through the dependent angle of the wound. No gauze pack is inserted unless there is bleeding that requires this maneuver for control.

Complete hemostasis is obtained. The exposure of the deep pelvis is complete (Fig. 7) and any residual oozing from the lateral veins can be easily controlled. The small intestine and omentum are then drawn down into the pelvis and both the abdominal and perineal wounds are closed. A rubber dam drain is placed in the hollow of the sacrum and brought out through the posterior portion

of the perineal wound. Closure of the perineal wound is accomplished by closing the subcutaneous fat in as many rows as possible with interrupted nonabsorbable sutures and closing the skin in a like manner. The abdominal wound is closed with interrupted figure-of-eight steel wire sutures. Following closure of the midline wound, both the colostomy and ileostomy are opened and the

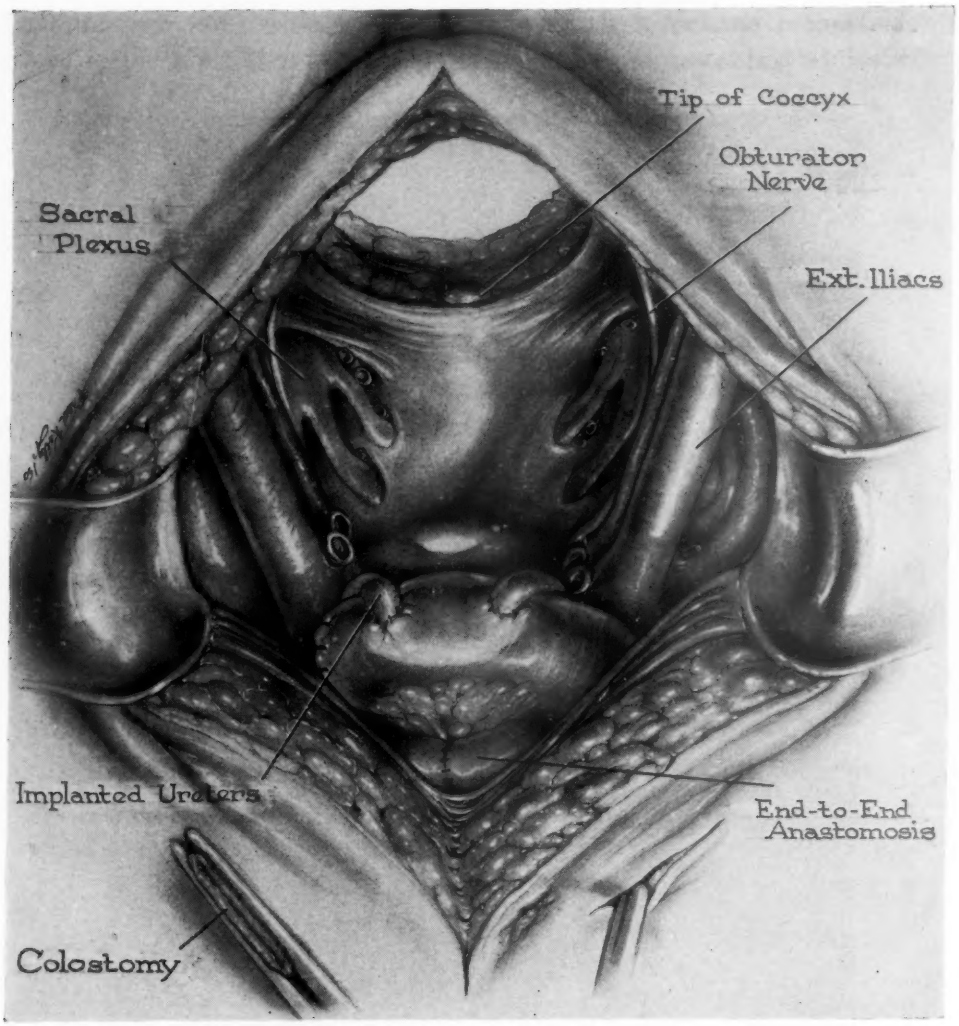

Fig. 8.—This illustration shows the completed dissection with the ureters transplanted to an isolated segment of terminal ileum. The ureteral transplantation and isolation of the ileum segment is done just prior to the performance of the perineal portion of the operation. The abdominal portion of the wound is closed with interrupted figure-of-eight steel wire sutures. The peritoneum of the lower portion of the abdominal wound has usually been removed and no attempt is made to reperitonize this area. After the abdominal wound has been closed, both the colostomy and ileostomy are opened and the mucosa is sutured directly to the skin with interrupted fine catgut sutures.

mucosa is sutured to skin with interrupted fine catgut sutures. A urethral catheter is inserted into the ileum segment for drainage of as much urine as will seek this path and to insure against the retention of urine in the segment in the early postoperative period.

The operation as described has consumed from five to seven hours operating time in our hands. Adequate blood replacement has averaged about seven to eight units.

Carcinoma of Rectum.—The procedure for carcinoma of the rectum differs in certain respects from the preceding description. Whereas with carcinoma of the cervix we have already decided that the bladder will be sacrificed if the lesion is resectable, the same is often not true with carcinoma of the rectum. In the attack on the cervix lesions the bladder is removed to facilitate a wide and complete dissection of the parametrial regions because it is in this direction that lymphatic spread is most likely. This is done whether or not there is actual invasion of the bladder. Carcinoma of the rectum, on the other hand, does not have such a propensity for lateral spread at this level and requires removal of the bladder only because of direct involvement of this organ at a level that makes it impossible to preserve the trigone with an adequate margin. Therefore, an important part of the initial survey and exploration of advanced rectal lesions suspected of involving the bladder will be determination of this fact. Ureteral catheters are in place to facilitate palpation. As a final step the bladder is opened and the trigone and ureteral orifices are inspected and palpated directly to determine whether or not they will have to be sacrificed.

Another difference in evisceration for rectal lesions lies in the fact that, since the tendency is for metastases to follow the superior hemorrhoidal vessels, the extreme lateral dissection as done for carcinoma of the cervix is omitted. Instead, the lateral plane of dissection is established medial to the hypogastric artery and interval iliac vein (Fig. 5). The hypogastric artery is ligated bilaterally for hemostatic purposes, but not resected.

Postoperative Care.—The patients are kept on continuous duodenal suction until it is positively evident that the end-to-end anastomosis of the small intestine is functioning, until peristalsis is normal, and until the colostomy is obviously serving to keep the bowel decompressed. This may mean a period of four to six days. This conservative attitude is adopted because it is felt that a complication in the form of ileus and abdominal distention or intestinal obstruction should be avoided at all cost. Daily enemas are started to the colostomy on the third postoperative day, first with mineral oil and subsequently with tap water or saline solution. A Rutzen type bag is applied to the ileostomy as early as possible, usually on the third or fourth postoperative day. An early application of the Rutzen bag serves to keep the patient dry and allows collection of all urinary output for measurement. The patient is placed on penicillin and streptomycin until the wounds are satisfactorily healed. Water and electrolyte balance is maintained and a blood transfusion is usually given on the third or fourth postoperative day. The perineal drain is left in place until it is determined whether or not the pelvic defect will be completely obliterated by descent of the small intestine. If the defect is completely obliterated, the drain is removed and the wound is allowed to heal. If it is felt by passing a clamp or the examining finger that a large defect remains, the drain site is kept open until the defect is obliterated. The majority of cases have been healed completely within a two-week period. An occasional case will require more

prolonged drainage and will necessitate attention to see that the drainage tract is kept open. Early ambulation is practiced, but in these cases it is usually not practical to get the patient out of bed into a chair until the second or third postoperative day. Intravenous pyelograms are made before discharge from the hospital.

SUMMARY

Pelvic evisceration would today appear to have a definite role in the treatment of advanced pelvic cancer but it must be emphasized that this type of surgery is as yet in an investigational phase. This is particularly true in carcinoma of the cervix, where irradiation methods remain the primary treatment of choice. Our own limited experience indicates that pelvic evisceration may prove of benefit as a salvage procedure in such patients who fail to be cured by irradiation methods.

The operation can provide a means of cure in certain cases of carcinoma of the rectum involving the genitourinary tract that in the past were regarded as inoperable.

Regarding the technical procedure, we do not believe that it is enough simply to accomplish the feat of removal of the pelvic viscera. This operation should be allowed the dignity of a careful selection of patients and of a technical performance that will fulfill the criteria of a cancer resection above and beyond that of mere magnitude of effort. Pelvic evisceration for recurrent carcinoma of the cervix can be a standardized controlled dissection comparable to other cancer procedures. The dissection should include the removal of the hypogastric artery and the internal iliac vein on both sides with all adjacent soft tissue and lymphatics. The operation cannot be considered as an adequate cancer procedure for recurrent carcinoma of the cervix unless all pelvic viscera are included in the removal.

In assessing the value of pelvic evisceration, it is important to survey critically from time to time those patients who fail to be benefited by the procedure. It is not enough to point up successful results in a procedure of this magnitude; these must be weighed against the over-all results.

If future studies reveal continued satisfactory results following the operation in patients with advanced recurrent carcinoma of the cervix, it is logical to predict that it may have a role as the primary method of treatment of certain other lesions that are known by experience to have little chance of being controlled by irradiation.

REFERENCES

1. Appleby, L. H.: Proctocystectomy: The Management of Colostomy With Ureteral Transplants, Am. J. Surg. **79**: 57-60, 1950.
2. Bricker, E. M., and Eiseman, B.: Bladder Reconstruction From Cecum and Ascending Colon Following Resection of Pelvic Viscera, Ann. Surg. **132**: 77-84, 1950.
3. Brunschwig, A.: Complete Excision of Pelvic Viscera for Advanced Carcinoma, Cancer **1**: 177-183, 1948.
4. Brintnall, E. S., and Flocks, R. H.: En Masse "Pelvic Viscerectomy" With Ureterointestinal Anastomosis, Arch. Surg. **61**: 851-869, 1950.
5. Parsons, L. G., and Bell, J. W.: An Evaluation of the Pelvic Exenteration Operation, Cancer **3**: 205-213, 1950.
6. Brunschwig, A., and Pierce, V. K.: Partial and Complete Pelvic Exenteration; A Progress Report Based Upon the First 100 Operations, Cancer **3**: 972-975, 1950.

7. Willis, R. A.: Pathology of Tumours, London, Butterworth & Co. Ltd., and St. Louis, 1948, The C. V. Mosby Company.
8. Muir, E. G.: Carcinoma of the Prostate, Lancet **1**: 667-672, 1934.
9. Higgins, C. C.: Total Cystectomy for Carcinoma of the Bladder, J. A. M. A. **135**: 619-622, 1947.
10. Jewett, H. J.: Infiltrating Carcinoma of the Bladder. Applications of Pathologic Observations to Clinical Diagnosis and Prognosis, J. A. M. A. **134**: 496-500, 1947.
11. Cordonnier, J. J.: Ureterosigmoid Anastomosis, J. Urol. **63**: 276-285, 1950.
12. Marshall, V. F.: A Comparison of Radiation and Surgery for Cancer of the Bladder, J. A. M. A. **134**: 501-507, 1947.
13. Leadbetter, W. F., and Cooper, J. F.: Regional Gland Dissection for Carcinoma of the Bladder: A Technique for One-Stage Cystectomy, Gland Dissection and Bilateral Uretero-Enterostomy, J. Urol. **63**: 242-260, 1950.
14. Rouviere, H.: Anatomy of the Human Lymphatic System, Ann Arbor, 1938, Edwards Brothers, Inc.
15. Cunningham, J. H.: Tumors of the Bladder, J. Urol. **25**: 559-587, 1931.
16. Spooner, A. D.: Epithelioma of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **27**: 81-89, 1934.
17. del Regato, J. A.: The Treatment of Carcinoma of the Cervix, Radiology **46**: 579-582, 1946.
18. Heyman, J.: Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix, Vol. 5, Stockholm, 1949, League of Nations Health Organization.
19. Ackerman, L. V., and del Regato, J. A.: Cancer: Diagnosis, Treatment and Prognosis, St. Louis, 1947, The C. V. Mosby Company.
20. Levin, M. L.: Cancer Reporting in New York State, New York State J. Med. **44**: 880-883, 1944.
21. Modlin, J. J.: Five Year Results of Treatment at the Ellis Fischel State Cancer Hospital, J. Missouri State M. A. **46**: 485-488, 1949.
22. Brunschwig, A., and Pierce, V. K.: Necropsy Findings in Patients With Carcinoma of the Cervix, Am. J. Obst. & Gynec. **56**: 1134-1137, 1948.
23. Morris, J. McL., and Meigs, J. V.: Carcinoma of the Cervix. Statistical Evaluation of 1,938 Cases and Results of Treatment, Surg., Gynec. & Obst. **90**: 135-150, 1950.
24. Sisson, R. J.: Personal commuication.
25. Heyman, J., and Belonoschkin, B.: Surgical Intervention in Recurrent and in "Radioresistant" Cancer of the Uterine Cervix, Acta chir. Scandnav. **98**: 489-496, 1949.
26. Bricker, E. M.: Bladder Substitution After Pelvic Evisceration, S. Clin. North America **30**: 1511-1521, 1950.

DISCUSSION

DR. HOWARD ULFELDER.—I am sure everyone here will agree with me that Dr. Bricker has this morning elevated this procedure to a real place in the treatment of pelvic cancer by making it a true cancer operation. These illustrations are the best that I have ever seen to prove that it is possible to get around these growths and their lateral extensions and their first chain of satellite lymphatics. It is really a thrill to be here this morning and see these illustrations and realize that the operation most of us have been doing has been to some extent incomplete laterally because it is almost purely by chance that we have in the past exposed all the digitations of the sciatic nerve.

We have had some experience, of course, with this at the Massachusetts General Hospital. We are fond of this operation in a very selected group of patients and we have some very gratifying results and some very satisfied individuals who have been subjected to this procedure, chiefly, of course, in the cancer of the cervix group. We do have a few patients with carcinoma of the rectum who have been benefited in the same way. I must agree wholeheartedly with Dr. Bricker's statements that operability at the present time cannot be judged without abdominal exploration. We too have had the experience of finding cases about which we were most pessimistic preoperatively prove to be extremely simple dissections once the operation was in progress. I also must agree wholeheartedly with his observation that trying to save either the rectum or the bladder is fraught with an extremely high incidence of recurrence of the disease. In our experience no patient with carcinoma of the cervix in whom the rectum was saved because the tumor appeared to be entirely an anterior one has survived without recurrence. I know this is not Dr. Brunschwig's experience. He has had some individuals apparently relieved for quite a while by the so-called anterior resection, but we have not been so fortunate.

There is one modification of the operation that I should like to mention at this time. It seems to be backtracking somewhat on Dr. Bricker's contention that a radical excision is necessary, but we have found in a considerable number of these patients that we can limit the procedure to an abdominal removal by amputating the pelvic viscera at a level just below the levator muscles. So far we have not regretted this. This, of course, is not our routine procedure; if there is any question whatsoever about extension of the disease downward along the vagina or paravaginal tissues the combined abdominal and perineal procedure is carried out. But in a great many of these patients the tumor extension appears to have been entirely laterally and upward and we have found that we have decreased the morbidity and mortality of the operation in those patients in whom it has been possible to do it entirely from above.

I certainly enjoyed Dr. Bricker's presentation.

DR. FREDERICK E. KREDEL.—I wish to propose in all seriousness that pelvic evisceration is not necessarily the most radical operation that you can conceive. Even if there may be fixation in the pelvis, involvement of the external iliacs or inguinal regions, there is still the theoretical possibility of operative removal by pelvic amputation, simply a halfectomy. Secure the terminal aorta and vena cava and the rest of the operation would be relatively simple. Simply divide the vertebral column, secure the dura, and what not.

May I have that slide, please. It is a horrible thought to be sure, but I have done this suprapelvic amputation on a cadaver and that would be the result. I believe you could fit a prosthesis on this and make a decent living individual. It was disappointing, though, when we put radioactive phosphorus in the embalming fluid in this cadaver, that the circulation in those flaps was rather poor. So you'd probably have to do this in two stages.

DR. EUGENE M. BRICKER (Closing).—I wish to thank the discussors. I am glad that the procedure described by Dr. Kredel has finally been brought to light. It was inevitable that the gruesome possibility would occur to others, as it has occurred to me. I have been afraid to mention it in public for fear of being taken seriously.

RADIOACTIVE COBALT AS AN ADJUNCT TO CANCER SURGERY

ARTHUR G. JAMES, M.D., ROGER D. WILLIAMS, M.D., AND
JOSEPH L. MORTON, M.D., COLUMBUS, OHIO

(From the Departments of Surgery and Radiology, University Hospital, Ohio State University College of Medicine)

IT IS well known that surgery, regardless of how extensive, is not sufficient in the treatment of all cancer. In those cases in which cancer tissue cannot be totally excised, some form of radiation may enhance the possibility of cure. In the past this has been accomplished by the use of radium or by x-ray. Both of these agents have their limitations. During the past 3 years studies have been under way at the Ohio State University[1, 2, 3] to develop methods by which radioactive cobalt might be used interstitially to supplant radium. Radioactive cobalt was selected as the isotope of choice because of the following advantages over radium:

1. Penetrating beta rays are more easily completely filtered. It is therefore possible to radiate cancer tissue near bone more safely with cobalt than with radium.

2. Cobalt lends itself to use in multiple weak sources which make possible heavy treatment close to previously irradiated tissues by means of accurate dosage control.

3. The thin, flexible, nylon applicator that encases the cobalt can be used in an irregular volume of tumor tissue and can be patterned to give a uniform and yet an effective level of radiation to the entire tumor.

4. The cost of cobalt is less than that of radium. At the present time, the cost is merely that of shipping and handling. This makes it easily possible for more cancer centers to have a sufficient amount of interstitial applicators.

5. It is simply calibrated by the use of the electroscope.

6. It is easier to handle since it is a magnetic metal and can be handled with a small electromagnet.

7. It is safer to handle since it does not form gaseous radioactive products on decay and there is no powder to become absorbed in case of breakage.

TYPES OF APPLICATORS

Radioactive cobalt applicators were first made in the form of needles fashioned from stainless steel or Monel tubing. It soon became apparent that clinical situations were encountered which could not be satisfactorily implanted with rigid needles. Many of the clinical problems which arose suggested the need for a flexible "linear" source which could be made to follow the contours of tumor infiltration. Subsequently, Co^{60} was cut in small lengths of about 3 mm. and encased in flexible nylon tubing[3] (Fig. 1). The wall of this tubing was sufficiently thick to filter out all but insignificant amounts of the beta particles emitted by the cobalt. Because of the flexible properties of the nylon tubing,

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patients were more comfortable following implantation than they were with the rigid needles. This new applicator also made it possible for the therapist to achieve a more uniform and effective pattern of radiation in many areas than would otherwise have been possible.

The loaded nylon applicators may be implanted into any site to be irradiated, which can be reached by long, straight Keith or curved tension needles (Fig. 1), or by straight or grooved pointed guides used like aneurysm needles. In cases in which the pattern is complex it is advisable to insert the guide

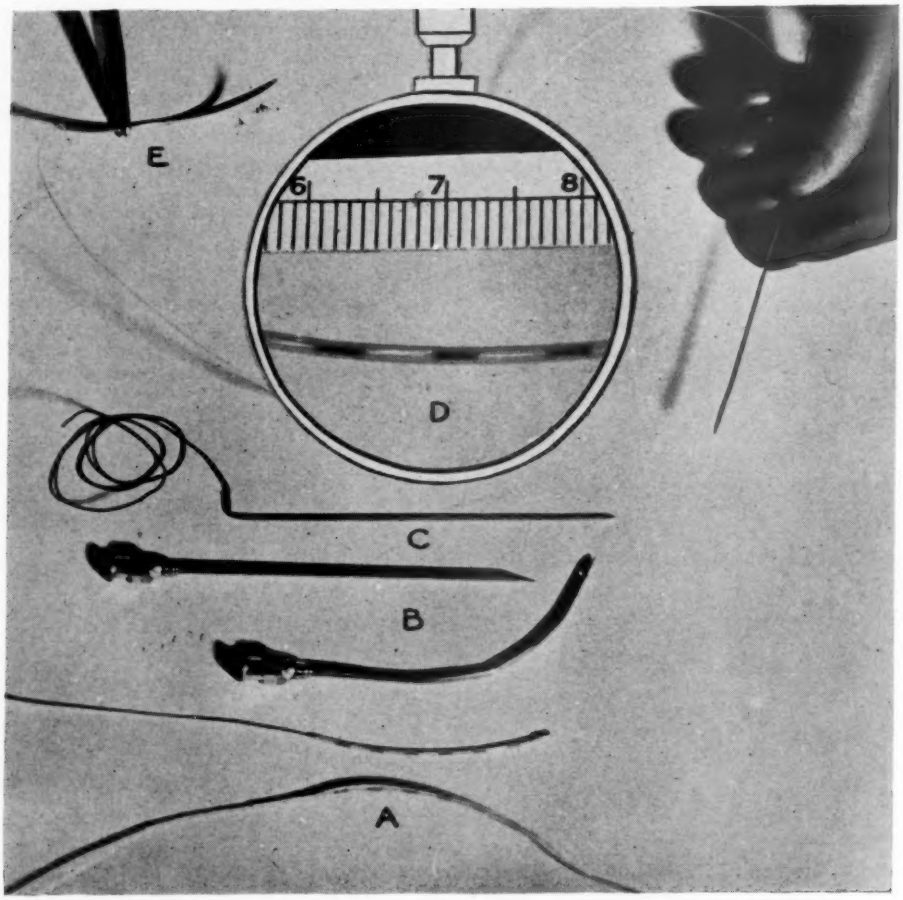

Fig. 1.—Types of Co^{60} applicators and guide needles. *A*, Flexible nylon tubes; *B*, curved and straight grooved guide needles; *C*, rigid aluminum needle containing Co^{60}; *D*, magnification of nylon tube (the darker segments represent the Co^{60} in 3 mm. lengths); *E*, curved and straight guide needles.

needles by hand or with instruments and to complete the entire pattern with the surgical needles in position before threading the nylon onto them. The radioactive "sutures" are then quickly drawn into position and the exposure to the hands of the operator is minimized.

As each case presents itself, it is considered individually and the best possible pattern of irradiation is planned by the Radiology Department. The larger the implantation, the more critical is the need for an accurate uniform

irradiation to all the tumor (Fig. 2). In addition to preplanning each problem, a sufficient amount of loaded nylon tubes is kept on hand so that they can be used on very short notice when the surgeon discovers that he has unexpectedly encountered a nonresectable tumor. Under such circumstances the cobalt sutures are spaced about 1 cm. apart throughout the tumor tissue.

CLINICAL MATERIAL

During the past year radioactive cobalt has been implanted in 53 cases of general surgical interest. Thirty-eight of these were in the head and neck regions, 8 in the abdomen, 4 in the chest, and 3 in the extremities. For the most part, this cobalt was used because the lesion was not completely resectable.

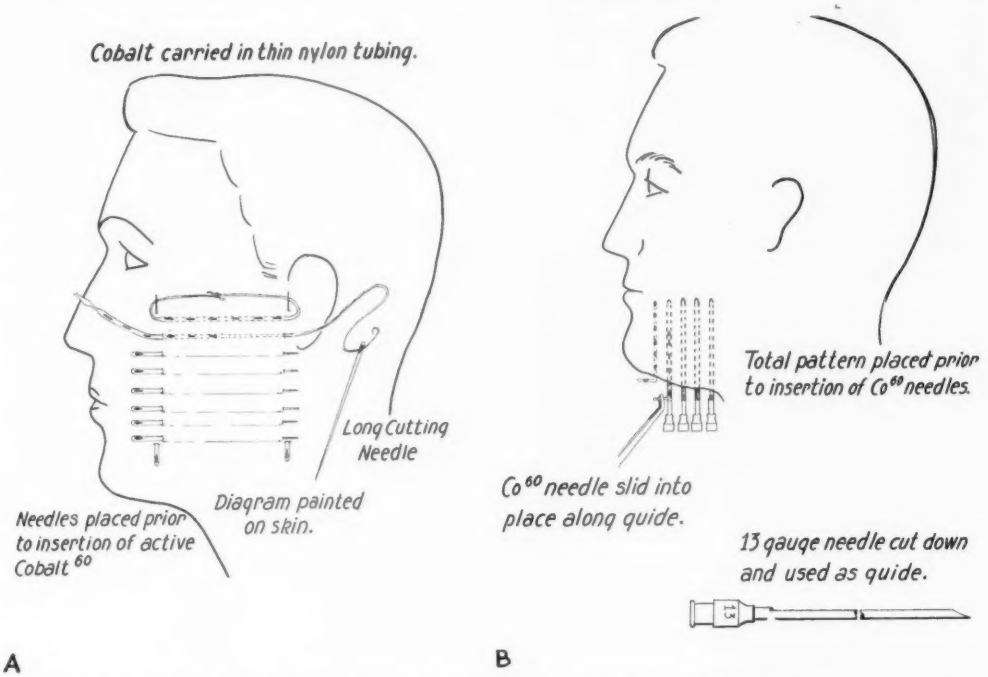
Cobalt carried in thin nylon tubing.
Long Cutting Needle
Diagram painted on skin.
Needles placed prior to insertion of active Cobalt 60
A
Total pattern placed prior to insertion of Co60 needles.
Co60 needle slid into place along guide.
13 gauge needle cut down and used as guide.
13
B

Fig. 2.—Cobalt applicators being inserted. *A*, Implantation technique, flexible nylon threads; *B*, needle technique, using rigid needles. Note that the pattern is first obtained with empty guide needles 1 cm. apart before the Co^{60} applicators are pulled into place.

The age variation of this group of patients was from 17 to 92 years with an average of roughly 59 years. Nylon tube applicators were used in 34 cases, aluminum needles in 12, conjunction of nylon tubes and needles in 3, and superficial plaques in 4.

The pathologic diagnosis was squamous-cell carcinoma in 37 cases, adenocarcinoma in 8 cases, sarcoma in 4 cases, lymphosarcoma in 3 cases and basal-cell carcinoma in 1 case.

Head and Neck.—Our greatest experience with the use of radioactive cobalt has been in the head and neck areas. Many of the malignant tumors in these regions are best treated by surgical excision. Postoperative radiation is used in those cases in which there can be only incomplete resection of the tumor. Radioactive cobalt should have a larger use in these regions because: (1) it can

be better used in irregular masses of tumor tissue than any other form of interstitial radiation that we have at the present time; (2) it can be used with less morbidity in the vicinity of bone than can radium; and (3) it can be used effectively in some cases which have been treated heavily with external radiation to skin tolerance. The following brief case reports represent examples of how radioactive cobalt is used in these regions.

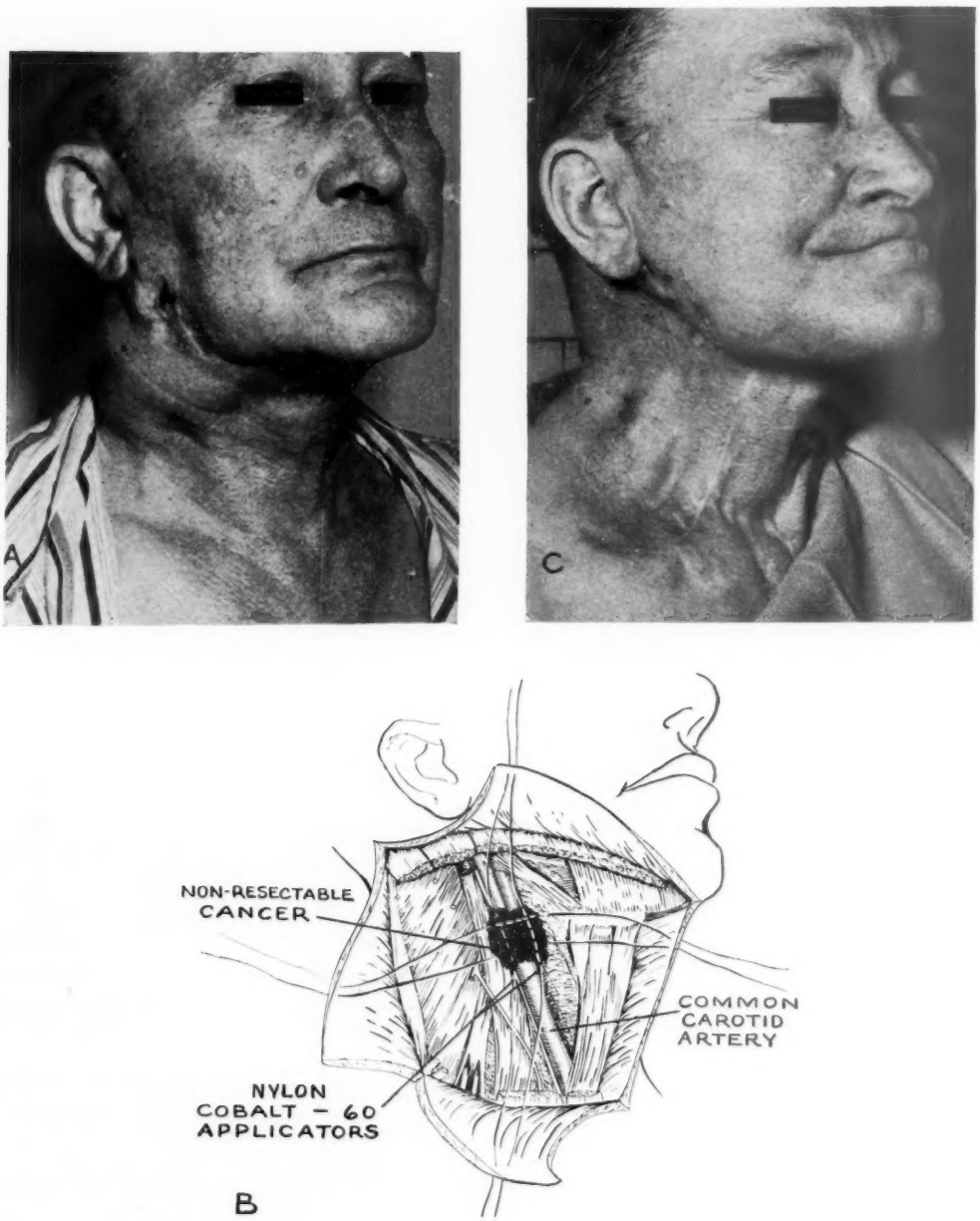

Fig. 3.—*A*, Showing bulky metastatic carcinoma in the neck. *B*, After neck dissection, showing tumor invasion of carotid bulb. Co^{60} in nylon tubes has been implanted. *C*, Seven months after neck dissection and radioactive cobalt implantation.

CASE 1.—C. N. (No. 50264A), a 60-year-old white man, was admitted to the University Hospital May 3, 1950, with a mass in the right side of the neck (Fig. 3, *A*) and an ulcer on the lower gingiva. The mass in the neck had gradually increased in size so that on admission it filled most of the upper neck. It measured approximately 10 by 8 by 6 cm., and was adherent to deeper structures. The gingival lesion measured about 2 by 3 cm., was ulcerated, and was located in the anterior part of the floor of the mouth near the gingiva of the lower jaw. The lesions were biopsied and both showed squamous-cell carcinoma. On May 5, 1950, the mouth lesion was excised and a right radical neck dissection was performed. A mass of tumor tissue about 3 cm. square was found to encase the carotid artery and its divisions (Fig. 3,*B*). Rather than sacrifice these vessels and risk the high resulting morbidity in this age group, Co^{60} in nylon tubes was implanted in planes surrounding the vessels.

In this manner it was possible to deliver 10,000 roentgens directly into the tumor mass. Good regression was obtained and, to date, there is nothing suspicious of cancer in this area (Fig. 3, *C*). It is doubtful that this case could have been locally controlled with any other treatment. The fact that the applicators are flexible made it possible to irradiate completely the tumor tissue in a uniform and adequate manner.

CASE 2.—E. W. (No. 493984C), a 56-year-old white man, was admitted to the University Hospital Aug. 6, 1949. He gave a 3 year history of a carcinoma of the right lower gingiva which had been treated at different intervals with x-ray therapy. Upon admission he presented an advanced process involving the right lower gingiva, the floor of mouth, cheek, and submaxillary lymph nodes. On Aug. 8, 1949, a right radical neck dissection was performed. The right half of the mandible including the involved cheek and floor of mouth was then excised. Healing was not delayed and the patient had no difficulty for several months. However, later he developed recurrent disease involving the cheek in the zygomatic region as well as the retromolar tissues. At this time it was felt that further excision was impossible. Since he had had heavy radiation, it was felt that only an insignificant amount of external radiation could be added. Radioactive cobalt in nylon tubes was implanted uniformly throughout the tumor tissue, and a total of 7000 roentgens was delivered.

There was good immediate regression and good healing; however, the patient finally succumbed from further recurrence of the disease. This case illustrates the possibility of using radioactive cobalt when it is not possible to do further surgery, and also when external high voltage radiation or radium cannot be used in any great amount because of previous skin irradiation.

CASE 3.—N. C., a 69-year-old white woman, was first seen in the X-Ray Department of the University Hospital in May, 1949. She presented an advanced basal-cell carcinoma of the right orbit which had previously been treated elsewhere by escharotics. Active basal-cell carcinoma was still present and in close proximity to bone. She was treated with 3,600 roentgens of high voltage x-ray and then a moulage was made containing cobalt which was used as a surface applicator. Five thousand additional roentgens were delivered in this manner. There was good regression of tumor and no resultant bony breakdown.

This case demonstrates another definite advantage of cobalt—that of being able to radiate, heavily, cancer tissue near bone. This is possible by careful dosage control because there is no selective absorption of the hard gamma ray in bone.

Abdomen.—Most of the tumors that occur in the abdomen are comparatively radioresistant. To date there is very little to offer the patient who develops metastatic adenocarcinoma in the retroperitoneal lymph nodes when they are adherent to the major vessels. Surgical excision is not feasible. External high voltage radiation delivers an inadequate dose to the tumor proper. Again radioactive cobalt in nylon tubes can be readily applied to this region and a

heavy uniform dose delivered to the tumor. To date about 8 patients with abdominal cancer have had cobalt implanted into them. The following is an illustrative case.

G. C. (No. 507287A), a 64-year-old Negro man, was admitted to the University Hospital on Dec. 12, 1950. X-ray studies showed a carcinoma of the descending colon. Transverse colostomy was performed soon after admission. On Jan. 2, 1951, a partial colectomy was performed for carcinoma of the descending colon. At the time of operation several large

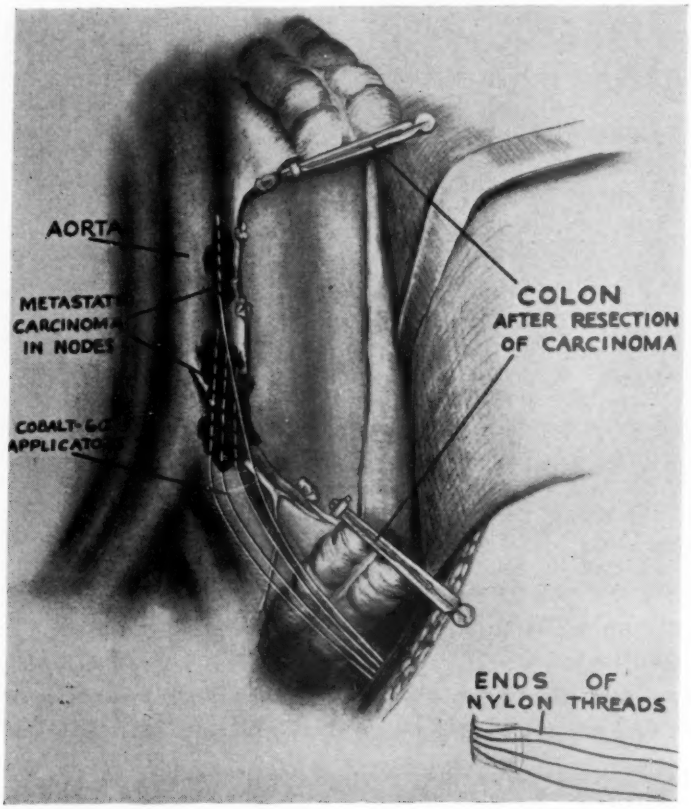

Fig. 4.—Co^{60} nylon applicators in place in metastatic adenocarcinoma in aortic lymph nodes from cancer of the sigmoid colon. Loose ends brought out through abdominal wall stab wound.

hard nodes were found overlying the aorta and adherent to the inferior mesenteric artery. Frozen section of these nodes showed metastatic adenocarcinoma. It was not feasible to resect those nodes because of their involvement of a major vessel. Therefore, 4 nylon threads containing 24 pieces of radioactive cobalt were implanted into the nodes and the free ends of the threads were brought out through a small stab wound in the left lower abdomen (Fig. 4). They were removed on the ward without anesthesia 7 days later, after delivering about 7,000 roentgens to the site of the metastatic tumor. No untoward reactions were noted. On January 22, 20 days later, at the time of closure of the colostomy, the abdominal cavity was re-explored. There had been regression of the nodes; however, brawny induration was present. There was some necrosis of a portion of the nodal masses present.

It is premature to say much more than that it is easily feasible to implant radioactive cobalt in nonresectable cancer tissue in the abdomen and that it is well tolerated in the peritoneal cavity. Time will be needed to evaluate the

results. This might be a very valuable agent to have at the time of "second and third looks" as advocated by the Wangensteen group[4] at the University of Minnesota School of Medicine. In case the recurrent cancer is not resectable at the time of re-exploration, the implanting of an agent which could deliver an adequate radiation dose to the entire tumor mass might salvage some of the otherwise hopeless cases.

Chest.—Carcinoma of the esophagus is a radiosensitive tumor. The results of surgical excision of this lesion as well as treatment with external heavy radia-

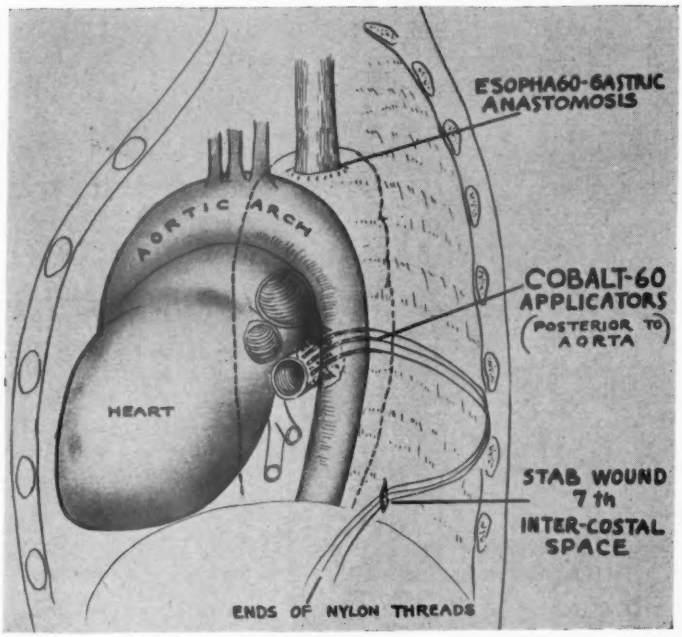

Fig. 5.—Co^{60} nylon applicators in place in nonresectable portion of carcinoma of esophagus invading main bronchus. Brought out through chest wall stab wound.

tion have been very poor. The reason is that there is early spread of disease to the regional nodes, and both of the preceding treatments are usually too limited in their scope. Radioactive cobalt should have much to offer in the treatment of this disease. Again, with the flexible nylon tubes it should be possible to radiate uniformly along a large part of the esophagus and along the involved mediastinal nodes. This same line of reasoning could be applied to hilar nodes that are involved from metastatic carcinoma of the lungs, since they are radiosensitive tumors. Our experience with the use of Co^{60} in this region has been very limited but the following is a case in point.

F. S. (No. 506732A), a 60-year-old white man, was admitted to the University Hospital Nov. 13, 1950, with a 6 week history of progressive dysphagia and inability to take liquids for 24 hours. He was proved to have a squamous-cell carcinoma of the esophagus. On November 27, a partial esophagectomy was performed, but since the tumor was densely adherent to the left main stem bronchus and to the arch of the aorta, it was felt that all of the tumor could not be excised. Four nylon sutures containing 24 pieces of Co^{60} were therefore sutured along the left main stem bronchus and brought beneath the arch of the aorta

(Fig. 5). The empty nylon ends were brought subpleurally to the lateral thoracic wall and out by way of a small stab wound just inferior to the thoracotomy incision. These nylon sutures were removed without anesthesia 7 days later. A total of 7,000 roentgens was delivered in the region of the primary tumor.

No untoward reactions to the cobalt were noted. Much work will have to be done in this area before the value of this agent can really be determined.

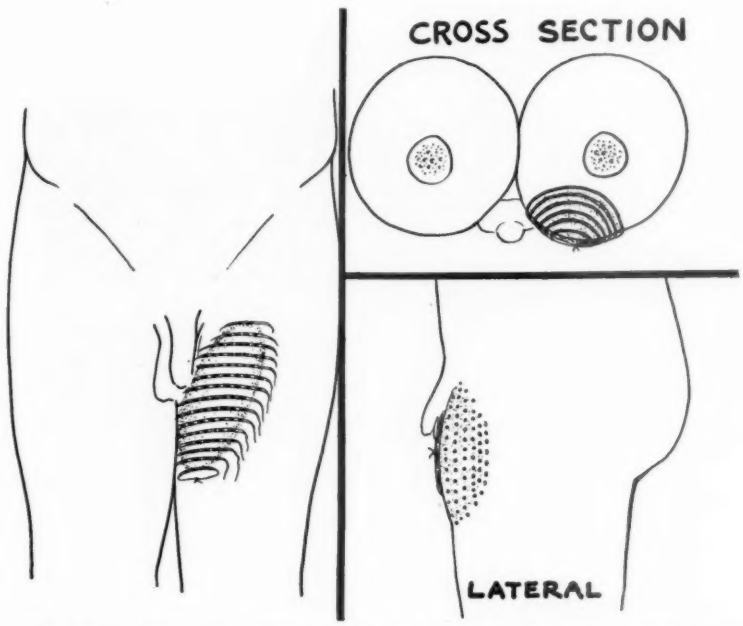

Fig. 6.—Schematic views of upper thigh with Co^{60} implanted into recurrent neurogenic fibrosarcoma. Note the uniform pattern of the implantation.

Extremities.—Malignant lesions of the extremities in general are best treated by surgical excision. Occasionally it is impossible to resect all the tumor and in such situations it is advisable to give radiation postoperatively. Occasionally, also, there is recurrence of disease after the region has once been radiated to skin tolerance. In such circumstances, radioactive cobalt is especially indicated. The following cases illustrate uses of it in the extremities.

CASE 1.—J. R. (No. 494323A), a 50-year-old white man, entered the University Hospital June 18, 1949, with a mass in the upper left thigh. In addition, the patient had multiple subcutaneous nodules typical of neurofibromatosis. The mass in the left femoral triangle was nontender, nonfluctuant, smooth, firm, slightly movable, and measured 10 by 12 by 8 cm. On June 22, 1949, the tumor, including the sartorius muscle, was excised. At that time it was noted that there was some adherence of the tumor to the femoral artery and vein. The pathologic diagnosis was neurogenic fibrosarcoma. The mass recurred and a biopsy on Feb. 23, 1950, again showed metastatic sarcoma. Thigh disarticulation was contemplated; however, the patient and his family would not consider surgery. Therefore, the lesion was irradiated with x-ray. A total of 3,250 roentgens was delivered to the tumor during March, 1950, with complete clinical disappearance of the mass. In the fall of 1950 the mass recurred again. On Nov. 12, 1950, it measured 14 by 6 by 6 cm. Since skin tolerance to x-ray therapy had nearly been reached, radioactive cobalt was implanted directly into the tumor mass on Nov. 13, 1950 (Fig. 6). A total of 8,000 roentgens was delivered to the tumor.

Fig. 7.—Squamous carcinoma on dorsum of hand of 92-year-old physician. *A* and *B*, Tumor on admission. *C*, Three weeks after Co^{60} had been used. *D*, Two months later. Good regression and healing resulted.

When the patient was last seen on Jan. 19, 1951, there was complete absence of the mass in the anterior left thigh and only moderate skin reaction.

Fig. 8.—Roentgenograms of hand shown in Fig. 7. Note the uniform pattern obtained with the implanted Co^{60}. Epithelioma of dorsum of hand; nylon thread and 3 needles through base. Co^{60} adapts easily to varied irradiation applications.

CASE 2.—S. M., a 92-year-old physician, was seen as an outpatient of the University Hospital in February, 1950, with a large tumor on the dorsum of the left hand (Fig. 7). Biopsy showed a grade 2 squamous-cell carcinoma. The patient refused surgical excision of the mass. Cobalt 60 was implanted (Fig. 8) and 7,000 roentgens were delivered to the tumor. There was complete regression of the tumor and no evidence of recurrence to date.

SUMMARY

1. Radioactive cobalt applied in nylon tubes provides an adequate, safe, and economical method of irradiation.

2. This method of irradiation is especially valuable in inoperable malignant tumors: those in inaccessible sites and more especially, those near large vessels, bone, or areas previously irradiated to the point of tolerance.

3. Radioactive cobalt in nylon tubes provides the surgeon, at the time of operation, with a readily accessible method of heavily irradiating deeply seated residual malignant tumors in the abdomen and thorax.

4. Clinical examples have been cited demonstrating the applications of radioactive cobalt.

5. This method of irradiation appears worthy of further clinical trial. Long-term observations will be required to determine its efficacy in the treatment of otherwise hopeless cases.

REFERENCES

1. Myers, W. G.: Applications of Artificially Radioactive Isotopes in Therapy. I. Cobalt 60, Am. J. Roentgenol. **60**: 816, 1948.

2. Callendine, G. W., Jr., Morton, J. L., and Myers, W. G.: Physical Considerations in Applying Cobalt 60 to Cancer Therapy, Nucleonics **7**: 63, 1950.

3. Morton, J. L., Callendine, G. W., Jr., and Myers, W. G.: Radioactive Cobalt 60 in Plastic Tubing for Interstitial Radiation Therapy, Radiology **56**: 553-560, 1951.

4. Lewis, J. F.: Exploration Following Resection of the Colon, Rectum or Stomach for Carcinoma With Lymph Node Metastases. Read at the Thirty-Sixth Annual Clinical Congress of America College of Surgeons, Boston, October 27, 1950.

DISCUSSION

DR. ELDRIDGE CAMPBELL.—I would like to ask what effect this massive irradiation has on adjacent blood vessels.

DR. ARTHUR G. JAMES (Closing).—To date, with the dosages I have talked about, we have seen no harmful effects to the major vessels. The common carotid artery, on 2 different occasions, has been subjected to complete encircling with the nylon applicators and a total of 10,000 roentgens delivered to that area. At the present time we are conducting animal studies to determine what maximum amount of radiation the various large vessels can tolerate.

A CRITIQUE OF ANTERIOR RESECTION IN THE TREATMENT OF CANCER OF THE RECTUM AND PELVIC COLON

J. Englebert Dunphy, M.D., and Earl G. Broderick, M.D., Boston, Mass.

(From the Surgical Service, Peter Bent Brigham Hospital, and the Department of Surgery, Harvard Medical School)

DESPITE sporadic enthusiasm on the part of a few surgeons for procedures which spare the anal sphincter, a combined abdominal and perineal resection stands out as the safest and most effective operation for the arrest of cancer which arises in the lower 10 cm. of the rectum. However, a justifiable difference of opinion still exists regarding the proper management of cancer of the upper rectum and lower pelvic colon. Many surgeons feel that the radical abdominoperineal approach is as necessary here as it has been shown to be for lesions in the lower rectum. Others, notably Dixon,[6] have advocated an abdominal resection for cancer as low as 6 cm. from the anal canal. Although it is still too early to assess the long-range effectiveness of abdominal resection when compared with abdominoperineal resection for cancer of the lower pelvic colon and upper rectum, certain specific indications for its use can be formulated. The present study is directed toward this end.

TECHNIQUE

The term anterior resection has been applied to abdominal resection of the rectum for such a long time that it should be retained but because it is sometimes misconstrued as implying a segmental resection of the pelvic colon it requires definition. Properly executed it includes mobilization of the pelvic colon and rectum to the coccyx behind and the prostate or vagina anteriorly, a high ligation of the inferior mesenteric artery, and an excision of the same extent of mesentery and nodes as is accomplished in the abdominal part of a Miles resection. The variable branches of the middle hemorrhoidal artery may or may not be divided, depending largely upon their relation to the position of the lesion being resected.

Although the technique of this procedure is well illustrated in the literature, several points merit emphasis. The blood supply is variable and cannot be determined arbitrarily by the division of the bowel at any set point. The first consideration is not blood supply but an adequate cancer operation. Having done so, the viability of the remaining colon and rectum should be established and then the anastomosis performed if it is feasible. The pulsation of the vessels in the mesentery and the color of the bowel are adequate guides to its vascularity proximally. Distally, however, there is no mesenteric attachment and the bowel may have little or no serosal covering. Therefore, the determination of viability rests upon the demonstration of adequate bleeding from the cut edge of the rectal stump and for this reason an open anastomosis without the use of a crushing clamp is essential. A preliminary colostomy, formerly regarded

Read at the meeting of the Society of University Surgeons, Durham, N. C., Feb. 8-10, 1951.

as essential, is no longer necessary unless there is obstruction. The performance of a proximal vent to decompress the bowel may be omitted after the anastomosis in favorable cases. Since 1945 we have rarely employed a proximal colostomy.

MORTALITY AND MORBIDITY

The position of any operation in the surgeon's armamentarium is determined in part by its morbidity and mortality. It has been argued that anterior resection is a less formidable procedure than an abdominoperineal resection. This was true of the old Hartmann operation in which continuity of the bowel was not reestablished. However, a low anastomosis introduces the dangers of posterior space infection, peritonitis, fistula, and stricture, and some authorities have felt that these complications would make anterior resection more hazardous than an abdominoperineal resection.

The operative mortality in a representative series of anterior resections collected from the literature is shown in Table I. Experience with the procedure would seem to be a significant factor in reducing the number of fatalities. Both

TABLE I. MORTALITY IN ANTERIOR RESECTION

AUTHOR	CASES	DEATHS	
		NUMBER	PER CENT
Dixon	426	25	6
Fallis	31	2	6
Garlock			
private	128	6	5
ward	35	6	17
Gray	74	3	4
Koch	66	20	30
Morgan, Lloyd-Davis	81	6	7
Peter Bent Brigham Hospital	38	4	11
Wangensteen	71	4	6
Total	950	76	8

Dixon[6] and Wangensteen[21] in their earlier cases recorded a mortality of 10 per cent. In Garlock's series of ward cases performed by residents or occasional operators the mortality was 17 per cent. Although none of the deaths in our series was due to intraabdominal causes, the mortality of 11 per cent is con-

TABLE II. ANTERIOR RESECTION; CAUSES OF DEATH

AUTHOR	DEATHS	ETIOLOGY			
		ABDOMINAL SEPSIS	PULMONARY	CARDIAC	OTHERS
Dixon	25	13	4	2	6
Fallis	2	1			1
Garlock	6	2	2		2
Gray	3	1	1		1
Koch	20	8	6	6	
Morgan, Lloyd-Davis	6	2	1	1	2
Peter Bent Brigham Hospital	4		2	2	
Total	66	27 (41%)	16 (24%)	11 (17%)	12 (18%)

siderably higher than that for resection and primary anastomosis elsewhere in the colon. The nature of the deaths (Table III) may reflect the rather long time required to complete an anastomosis in the hollow of the sacrum.

The causes of death following anterior resection are tabulated in Table II. As might be expected, sepsis stands out as a particular hazard. This has been reduced considerably since the antibiotics and improved methods of preoperative preparation of the bowel became available but, as Dixon[6] pointed out, it has not been eliminated. Although sepsis did not occasion a single death in our series, it was responsible for a considerable morbidity.

The morbidity which follows anterior resection cannot be accurately assessed from a review of the literature. There is a tendency for those experienced in its use to regard it as occasioning less hospitalization and fewer postoperative sequelae than an abdominoperineal resection. However, this impression is not entirely substantiated by a study of the available data. Dixon,[6] who usually employs a proximal colostomy, spoke of closing it within 3 to 4 weeks which means a total hospital morbidity of approximately one month in favorable cases. Not infrequently, as he pointed out, a delay in closure is necessary because of a temporary fecal fistula. This view is supported by the high incidence

TABLE III. SUMMARY OF PETER BENT BRIGHAM HOSPITAL SERIES

Total cases:		38
Deaths		4
Causes:		
Coronary occlusion	2	
Pulmonary embolism	1	
Addisonian crisis	1	
Complications in 34 survivors		
Immediate septic:		
Rectovaginal fistula	1	
Pelvic abscess	2	
Intra-abdominal abscess	2	
Late septic:		
Stricture	2	
Local recurrence	3	
Survival periods		
Dead of disease within 2 yr.	12	
Less than 2 yr.	10	
Over 2 yr.	6*	
Over 3 yr.	1	
Over 4 yr.	2	
Over 5 yr.	3	

*Includes one patient with secondary abdominoperineal resection.

of infection and abscess formation which some operators have reported. In 65 per cent of Wangensteen's earlier cases some degree of posterior space infection was encountered.[21] In his more recent series these data are not given.[22] The average postoperative hospital stay in his earlier cases was 30 days. Morgan and Lloyd-Davis[18] reported a 12 per cent incidence of temporary fistula, infection, or stricture in the immediate postoperative period. Fallis[9] encountered stricture in 10 per cent of his cases and a permanent fecal fistula in 5 per cent.

In our series the incidence of these sequelae was as follows: Abdominal or posterior space infection 10 per cent, fistula 6 per cent, and stricture 3 per cent (Table III). Although one-third of the patients were discharged from the hospital in less than 3 weeks after operation, the average period of postoperative hospitalization was 30 days. The introduction of the antibiotics and improved methods of bowel preparation have improved these figures considerably. In the last 12 cases there have been no instances of fistula, pelvic abscess, or abdominal sepsis. However, one patient has developed a stricture and one has suffered from intractable diarrhea, probably a consequence of a very low anastomosis with loss of the normal anorectal reflexes.[11] There have been no deaths since 1948.

Although the morbidity and mortality of anterior resection are undoubtedly less today than the data in Table I indicate, it is evident that it is a formidable procedure and not one to be undertaken because it is easier or less hazardous than an abdominoperineal resection. On the other hand, while an anastomosis low in the pelvis presents technical difficulties which may lead to serious complications, sufficient data have accumulated to demonstrate that this is not a prohibitive hazard. In experienced hands the morbidity and mortality of anterior resection and abdominoperineal resection are approximately the same. The great advantage of anterior resection is that it restores the continuity of the bowel. Its use should rest on its adequacy as a cancer operation however and not on the assumption that it is easier on the patient.

IS ANTERIOR RESECTION AN ADEQUATE CANCER OPERATION?

The bugbear of anterior resection in the minds of most surgeons is its limited scope. The extensive studies of Dukes,[7] Gilchrist and David,[12] Coller and associates,[3] and Grinnell[14] on the manner of spread of cancer of the rectum have been used as evidence that an extensive resection distal to the lesion is not necessary. There is general agreement that distal lymphatic metastases are exceedingly rare in early cases and distal intramural spread is dismissed by most authorities as of no consequence. Black and Waugh[1] found that the histologic evidence of growth beyond the gross base of the neoplasm was always less than 2 cm. in the formalin-fixed specimen. They concluded that "Only 2 centimeters of normal bowel need be allowed above and below the lesion in order to remove the whole of the primary growth." Such studies have encouraged many operators to be satisfied with a limited resection in order to complete an anastomosis in the rectosigmoid area.

There are several reasons why the application of these pathologic findings to assess the adequacy of anterior resection may not be valid. First, it should be clear that a 2 cm. margin in the formalin-fixed specimen is a vastly different thing from a 3 cm. margin estimated by the surgeon while making traction on the viable bowel. We have found that the margin of normal bowel determined histologically in the formalin-fixed specimen is usually just about one-third as great as the estimate made by the surgeon as he places clamps on the viable bowel. In one instance an estimated margin of 10 cm. proved to be less than

2 cm. in the formalin-fixed specimen. For this reason we believe that the studies of Black and Waugh[1] should be interpreted as requiring an operative margin of not less than 5 cm. However, even this may not be enough in some cases. We have seen 2 cases in which intramural spread occurred in the left colon for distances of over 5 cm. beyond the base of the primary lesion. Monsarrat and Williams[17] have described such a case and more recently Connell and Rottino,[4] in an elaborate study, found that intramural distal extension occurred for distances of 3 to 7 cm. in nearly one-half of their cases.

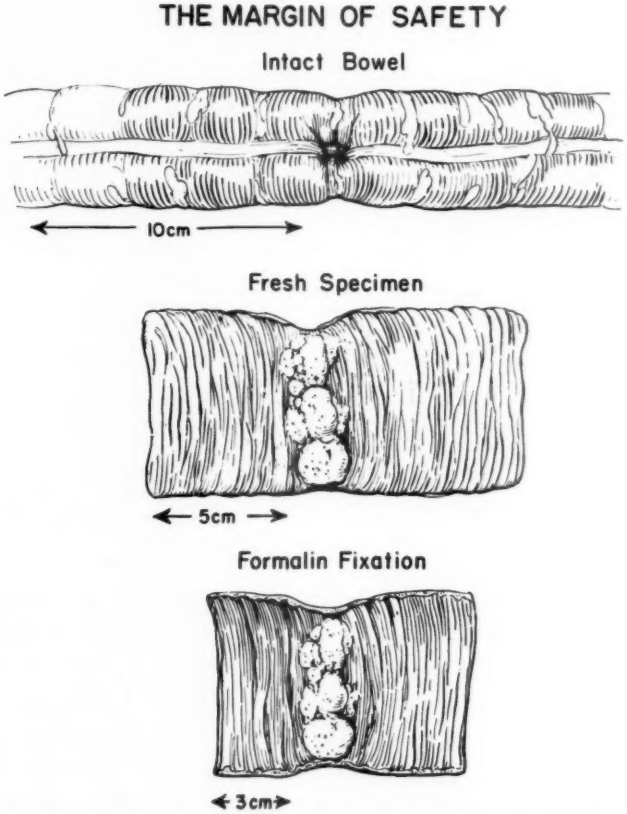

Fig. 1.—This sketch depicts the average discrepancy which arises between the surgeon's estimate of the margin of normal bowel obtained at operation and that demonstrable by microscopic examination of the formalin-fixed specimen. An estimate of 10 cm. is the barest minimum with which one should be satisfied.

There are additional reasons why the resection of normal bowel adjacent to a primary cancer should be made as wide as possible rather than limited in accordance with presumed spread based on histologic studies. Biologically, the distal colon is peculiarly vulnerable to neoplastic and polypoid degeneration. For this reason only, a wide resection is desirable. Finally, there is a theoretical factor to be considered. The mucosa of the normal bowel just distal to a primary growth is layered with neoplastic cells shed by the lesion. As Morgan and Lloyd-Davis[18] pointed out, incorporation of these cells in the granulation tissue of the suture line plus the trauma of suturing may be a factor which favors local implantation and recurrence. Theoretically, at least, the farther from the

lesion the anastomosis is performed, the less concentrated the shed cells will be. Morgan and Lloyd-Davis have thought it wise to irrigate the bowel prior to anastomosis in an effort to reduce this potential hazard.

Taking all these factors into consideration we believe that an operative "margin of safety" of 10 cm. is the minimal with which the surgeon should be satisfied. In the fresh pathologic specimen this will amount to a margin of 5 or 6 cm. and after formalin fixation the margin will hardly exceed the minimum required by the studies of Black and Waugh[1] (Fig. 1). The high incidence of local recurrences which have been reported following anterior resection makes this the minimum with which the operation can be considered adequate (Table IV).

TABLE IV. INCIDENCE OF LOCAL RECURRENCE FOLLOWING ANTERIOR RESECTION

AUTHOR	CASES	LOCAL RECURRENCE	
		NUMBER	PER CENT
Garlock	151	25	17
Gray	71	18	25
Morgan, Lloyd-Davis*	55	2	4
Peter Bent Brigham Hospital	34	3	9
Wangensteen*	63	7	11
Total	374	55	15

*Palliative operations excluded.

LOCAL RECURRENCES

Local recurrences are readily accepted as an indication of surgical failure in cancer of the breast and the same argument may be applied to carcinoma of the rectum. Table IV shows the incidence of local recurrence in 374 cases in which the data are sufficient to justify tabulation. Of the 55 patients in whom recurrence developed locally only 16 had operations which were regarded as palliative procedures. The rate of local recurrence varied directly with the level of the lesion. Wangensteen[22] found a recurrence rate of over 30 per cent where the operation was performed for lesions below 14 cm. from the anal canal. In Garlock and Ginzburg's series[10] the recurrence rate in this region was 37.8 per cent, whereas above 15 cm. it was about 5 per cent. These figures are particularly disturbing because, in general, anterior resection has been employed for the less extensive and more favorable lesions. Gilchrist and David[12] reported a 20 per cent incidence of local recurrences following the abdominoperineal operation including all types of cases and the lowest lesions. One cannot escape the impression, therefore, that some of the local recurrences which follow anterior resection could have been prevented by the abdominoperineal operation.

A substantial number of local recurrences amenable to an abdominoperineal resection would provide convincing evidence of the inadequacy of anterior resection in these cases. Cattell[2] and Crile[5] have encountered a number of such cases but the original operations were performed elsewhere and their adequacy could not be thoroughly assessed. Garlock and Ginzburg[10] found only one case in their series in which a local recurrence could be removed by an abdominoperineal resection. One of the 3 recurrences in our series belongs in this category and is of sufficient interest to warrant a brief description.

CASE REPORT

A 68-year-old woman entered the hospital because of intermittent diarrhea, constipation, and the passage of blood by rectum of 1 year's duration. Physical examination was essentially negative. Sigmoidoscopy disclosed a polypoid lesion 15 cm. from the anal canal and this finding was confirmed by a barium enema. After suitable preparation an anterior resection was performed in March, 1947. The lesion mobilized well and the estimated surgical margin of normal bowel distal to the lesion was 8 cm. The pathologic margin in the formalin-fixed specimen was estimated at 4 cm. There were metastases to 2 lymph nodes out of a large number examined.

The patient made an uneventful convalescence and was discharged from the hospital on the tenth postoperative day. Six months later, in the course of a routine follow-up, a firm, tender nodule was palpable 6 cm. from the anal canal posterior to the rectum. Sigmoidoscopic examination revealed normal mucosa overlying the nodule. Operation was advised but declined by the patient until she developed severe perineal pain. One year later, 21 months after the original anterior resection, the patient consented to operation and an abdominoperineal resection was performed in November, 1948. No evidence of distant or general metastases was found.

Pathologic examination of the specimen disclosed a mass of solid tumor 6 cm. from the anal canal. It had invaded the rectal mucosa from outside the rectal wall by the time of the operative excision. The lesion lay 6 cm. distal to the previous anastomosis. Judged by the surgeon in the operating room, the recurrence developed a total distance of about 14 cm. distal to the line of the original tumor.

The patient continued to suffer from moderately severe pain in the perineum and because of this re-exploration of the hollow of the sacrum was carried out one year following the abdominoperineal resection. No evidence of neoplasm was found. At the present time, 2 years since the abdominoperineal resection was performed, this patient is well and free of signs of recurrence.

There are 2 possible explanations for this recurrence. It may have been due to retrograde metastases far beyond that usually thought to occur in carcinoma of the rectum or it may have been caused by the implantation of tumor cells in the raw pelvic tissues at the time of the open anastomosis. Interpreted in this fashion it lends support to the views of Morgan and Lloyd-Davis[18] that implantation of viable cells either in the pelvis or in the suture line is responsible for some of these local recurrences. Regardless of the explanation, the result following abdominoperineal resection justifies the conclusion that if this operation had been performed in the first instance the local recurrence would have been avoided. In a small series such as ours the occurrence of only one case of this type warrants very careful selection of cases for anterior resection.

Sufficient time has not elapsed to present an appraisal of anterior resection on the basis of 5 year arrests. Our series and those of Fallis,[9] Gray,[15] Morgan and Lloyd-Davis,[18] Wangensteen and Toon,[22] and Garlock and Ginzburg[10] provide no conclusive data. Gray[13] and Koch[15] have recorded 42 per cent and 50 per cent 5 year survival in their cases but the only series of size is that of Dixon,[6] who reports a 67.7 per cent incidence of 5 year survivors in "nonpalliative cases." Although this is an extraordinarily good record it cannot be interpreted as conclusive evidence of the adequacy of anterior resection for low lesions. The high incidence of local recurrence which has been seen in most series within 3 years of operation (Table IV) indicates that Dixon's[6] remarkable record will not be duplicated. There are so many variables to be weighed, in-

cluding the experience of the operator, the selection of cases, particularly the manner of estimating the level of the lesion, and the pathologic grading of tumors, that a final estimate of the adequacy of the operation on the basis of 5 year arrests cannot yet be made.

THE INDICATIONS FOR ANTERIOR RESECTION

There is an aggregate of evidence which warrants caution in accepting anterior resection as an adequate cancer operation. It is a technically difficult operation and from the viewpoint of removing the cancer may not be as well performed in the hands of the occasional operator as an abdominoperineal resection. Pathologic studies are not entirely reassuring in regard to the validity of limiting the resection of normal bowel distal to the growth. The high incidence of local recurrence is particularly disturbing and in the occasional case the evidence indicates that an abdominoperineal resection might have prevented such recurrence. Finally, there are cogent theoretical reasons for making colon resections as wide as possible in every case, an advantage which the abdominoperineal will always have over the more limited anterior resection.

In the face of this evidence we feel that the use of anterior resection should be restricted to the following specific indications:

1. *To extend the scope of resection in cancer of the sigmoid.* We called attention to the use of anterior resection for this purpose a decade ago.[8] Although it has not been routinely employed by us it is a significant fact that 2 of the 3 five-year survivals which have accrued to date in our series fall in this category. More recently, McKittrick[16] and Grinnell[14] have recommended that anterior resection be routinely adopted for the resection of tumors of the lower sigmoid. This is now being done in our clinic and it may be that this indication will constitute a principal place for the operation of anterior resection in the future.

2. *To avoid colostomy in the presence of distant metastases from cancer of the upper rectum or rectosigmoid colon provided the local disease can be extirpated.* Considerable emphasis must be placed on an adequate local extirpation of the lesion. In our experience the results of palliative anterior resection where the local disease is not extirpated have been distressingly bad. Although a colostomy is avoided temporarily the anastomosis soon becomes involved with recurrent disease and the last state of the patient is worse than the first. Consequently, unless the local disease can be widely removed, an abdominoperineal resection provides much more effective palliation. The presence of hepatic or other distant metastases in cases in which the local disease can be readily removed is the ideal indication for anterior resection as a palliative operation. Here the avoidance of a colostomy is justifiable.

3. *To avoid colostomy in the elective surgery of cancer of the lower pelvic colon and upper rectum, provided a 10 cm. operative margin of normal bowel can be resected distal to the tumor, the pelvic fascia is not invaded by neoplasm, and there are no obvious lymph node metastases.* In actual practice this means that the lesion should not lie below the peritoneal reflection and that

in most instances the surgeon is dealing with a grade 1 lesion. The excellent results obtained by Dixon[6] justify a continued general use of anterior resection under these circumstances. The experiences of Garlock and Ginzburg[10] and Wangensteen and Toon[22] also support this approach. Their best results were obtained in lesions above 15 cm. from the anal canal. Morgan and Lloyd-Davis[18] also have urged that the operation be limited to lesions which do not invade the fascia propria and which lie above the peritoneal reflection. The most recent experiences of the St. Mark's group indicate that with these limitations the high incidence of local recurrence will be avoided.

If there are obvious metastases to nodes the likelihood of retrograde metastases is increased and under these circumstances the abdominoperineal resection should be employed.

Assuming that there are no nodes, we have chosen to place the emphasis on the extent of normal bowel which can be obtained below the lesion rather than on the level of the tumor as determined by sigmoidoscopic examination. Occasionally tumors arising over 20 cm. from the anal canal can be visualized by the sigmoidoscope at less than 15 cm. from the anus because of an accordion-like shortening of the bowel. Contrariwise, lesions above 15 cm. may present such technical difficulty to the surgeon, particularly in the obese patient, that an adequate margin of normal bowel is not removed below the tumor. Grinnell[14] has emphasized the scanty margin which anterior resection frequently provides in contrast to resection elsewhere in the colon. Consequently, to insure an adequate resection, the final decision to carry out anterior resection should be made after the rectum has been mobilized. If a segment of normal bowel equal to the width of the hand can be obtained distal to the lesion the surgeon is fully justified in carrying out an anterior resection, provided, of course, the lesion is not so low that the pelvic fascia is invaded. If the surgeon accepts a lesser margin the responsibility for local recurrence rests entirely upon his shoulders.

SUMMARY

This paper attempts a definition of the indications for anterior resection in the treatment of cancer of the rectum and pelvic colon. Based upon a study of the literature and the experience of the Peter Bent Brigham Hospital staff, it concludes that this operation should be employed only: (1) to extend the scope of resection for lesions of the lower sigmoid colon, (2) to avoid colostomy in the presence of distant metastases provided that the local disease can be completely extirpated, and (3) to restore continuity of the bowel in carefully selected cases of cancer of the upper rectum and lower pelvic colon in which the pelvic fascia is not invaded, there are no obvious lymph node metastases, and there is a minimal "operative margin" of 10 cm. below the tumor.

REFERENCES

1. Black, W. A., and Waugh, J. M.: Intramural Extension of Carcinoma of Descending Colon, Sigmoid and Rectosigmoid; Pathological Study, Surg., Gynec. & Obst. 84: 457-464, 1948.
2. Cattell, R. B.: Personal communication.

3. Coller, F. A., Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of Rectum, SURGERY **8**: 294-311, 1940.
4. Connell, J. F., and Rottino, A.: Retrograde Spread of Carcinoma in the Rectum and Rectosigmoid, Arch. Surg. **59**: 807-813, 1949.
5. Crile, G., Jr.: Personal communication.
6. Dixon, C. F.: Anterior Resection for Malignant Lesions of Upper Part of Rectum and Lower Part of Sigmoid, Ann. Surg. **128**: 425-442, 1948.
7. Dukes, C.: Surgical Pathology of Rectal Cancer; President's Address, Proc. Roy. Soc. Med. **37**: 131-144, 1944.
8. Dunphy, J. E.: Anterior Resection for Cancer of Rectosigmoid, Arch. Surg. **43**: 1076-1085, 1941.
9. Fallis, L. S.: Symposium on Surgical Management of Malignancy of Colon; Anterior Resection of Rectosigmoid and Upper Rectum With Re-establishment of Continuity, SURGERY **14**: 397-402, 1943.
10. Garlock, J. H., and Ginzburg, L.: An Appraisal of the Operation of Anterior Resection for Carcinoma of Rectum and Rectosigmoid, Surg., Gynec. & Obst. **90**: 525-534, 1950.
11. Gaston, E. A.: Fecal Continence Following Resections of Various Portions of Rectum With Preservation of Anal Sphincters, Surg., Gynec. & Obst. **87**: 669-678, 1948.
12. Gilchrist, R. K., and David, V. C.: Prognosis in Carcinoma of Bowel, Surg., Gynec. & Obst. **86**: 359-371, 1948.
13. Gray, J.: Evaluation of Conservative Resection With End to End Anastomosis for Carcinoma of the Rectum and Lower Sigmoid Colon, Arch. Surg. **57**: 361-372, 1948.
14. Grinnell, R. S.: Lymphatic Metastases of Carcinoma of Colon and Rectum, Ann. Surg. **131**: 494-506, 1950.
15. Koch, F.: A Contribution to the Operative Treatment (Resection) of Cancer of Rectum, Acta chir. Scandinav. **95**: 145-155, 1947.
16. McKittrick, L. S.: Principles Old and New of Resection of Colon for Carcinoma, Surg., Gynec. & Obst. **87**: 15-25, 1948.
17. Monsarrat, K. W., and Williams, I. J.: Intramural Extension in Rectal Cancer, Brit. J. Surg. **1**: 173-182, 1913.
18. Morgan, C. N., and Lloyd-Davis, O. V.: Discussion on Conservative Resection in Carcinoma of Rectum, Proc. Roy. Soc. Med. **43**: 697-710, 1950.
19. Newton, F. C., and Blodgett, J. B.: Succinylsulfathiazole and Intestinal Suction in Surgery of the Large Bowel, SURGERY **18**: 200-206, 1945.
20. Pemberton, J. de J.: Quoted by Dixon.[6]
21. Wangensteen, O. H.: Primary Resection (Closed Anastomosis) of Rectal Ampulla for Malignancy With Preservation of Sphincteric Function Together With Further Account of Primary Resection of Colon and Rectosigmoid and Note on Excision of Hepatic Metastases, Surg., Gynec. & Obst. **81**: 1-24, 1945.
22. Wangensteen, O. H., and Toon, R. W.: Primary Resection of Colon and Rectum With Particular Reference to Cancer and Ulcerative Colitis, Am. J. Surg. **75**: 384-404, 1948.

SURGICAL THERAPY FOR CHRONIC PANCREATITIS

RALPH F. BOWERS, M.D., MEMPHIS, TENN.

(From the Surgical Service, Veterans Administration Medical Teaching Group, Kennedy Hospital.)

CHRONIC inflammatory lesions of the pancreas are being diagnosed with increasing accuracy. Although interest and enthusiasm for surgery has increased, many surgeons fail to recognize the value of surgery and consequently remain skeptical of its use. They continue to associate surgery with the poor results obtained many years ago, when pancreatic surgery had not the advantages of safety and freedom from serious morbid states, and are still denying their patients operative procedures that are now known to be beneficial. This communication proposes to classify chronic pancreatitis into four workable types and to cite by example the benefits to be obtained by the use of the operations in these types of pancreatitis. Biliary tract surgery, sphincterotomy (Oddi), choledochojejunostomy, sympathectomy, cystenterostomy or cystgastrostomy, and partial pancreatectomy may be applied according to the pathologic condition present, with satisfactory results.

Classification according to type is as follows: (1) those cases in which relief is obtained by biliary tract surgery alone; (2) those cases that require prevention of regurgitated bile into the pancreatic duct under pressure—so-called chronic recurring pancreatitis; (3) those cases that demonstrate fibrosis and subsequent loss of active pancreatic tissue and that eventually show pancreatic deficiency—so-called "burned out" pancreas; (4) those cases of localized cysts or pseudocysts subsequent to acute pancreatic infection or trauma.

Cases Relieved by Biliary Surgery Alone.—There can be little doubt that many cases of chronic pancreatitis are encountered when there exists cholecystitis, cholelithiasis, common duct stone, or any combination of these three, with or without a demonstrable channel between the common and pancreatic ducts. The pancreatic phase of these cases is often not recognized clinically and is discovered at operation when the operator notices, in addition to biliary tract disease, induration, edema in the head of the pancreas, which sometimes involves the uncinate process, and, less often, a continuation of these findings into the body and the tail of the pancreas. Experienced operators have observed that the permanent results in these cases are not as good as in the gall bladder case when no involvement of the pancreas is present. After cholecystectomy some of these patients suffer typical gall bladder attacks, or indigestive symptoms or pain in the left abdomen with or without radiation to the left shoulder. The discomfort is intermittent and is sometimes labeled biliary dyskinesia or neurasthenia.

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The best results are obtained when the condition is recognized and common duct exploration and dilatation of the sphincter of Oddi with drainage of the common duct for a period longer than usual accompanies the cholecystectomy.

Gage and Floyd[1] stated that acute pancreatitis is produced by obstruction of the ampulla of Vater which forces bile under pressure into the pancreatic duct. Regardless of the anomalous arrangement of the ducts or the common channel that may be present, the bile cannot accumulate under pressure in the pancreatic duct without blockage of the ampulla of Vater. These writers also admit that spasm of the sphincter of Oddi is the contributing factor in a great number of cases. With the well-known association of pancreatitis and biliary tract infection and stones (60 to 80 per cent of the cases) it appears logical to assume that the sphincter spasm may be caused by the biliary tract disease. Also, it is a fact that many patients with proved recurring pancreatitis are relieved of their symptoms as long as common duct drainage persists. Consequently, cholecystectomy should be accompanied by common duct exploration, stone removal, dilatation of the sphincter of Oddi, and common duct drainage, The drainage tube remains in place for a period of one to three months, depending upon the intensity of the infection in the pancreas as revealed by palpation.

Accurate figures are not available to establish the efficacy of biliary tract surgery alone, because the frequency of pancreatitis in these cases is not accurately known. Undoubtedly, many cases are remedied by biliary tract surgery alone.

CASE REPORT

A 58-year-old white man endured three or four attacks of fairly typical gall bladder colic in the past two years. The patient had no indigestion or other trouble before this time. He was a nondrinker. At operation gallstones, induration, and edema in the head of the pancreas extending into body were found. There were no common duct stones. The common duct was explored, and the sphincter was dilated by passage of probes and catheters and drainage of the duct for a period of ten weeks. A cholangiogram postoperatively revealed an abnormal opening of the pancreatic duct into the common duct at a site proximal to ampulla of Vater. During a two-year, three-month follow-up there were no attacks of any sort.

Comment.—This case represents a patient with gallstones and an abnormal opening of the pancreatic duct into the bile duct. It is surprising that the patient did not suffer attacks earlier in life. We cannot state that the patient may have suffered postoperative attacks if choledochotomy, dilatation and drainage had not been accomplished, but these procedures can be done with safety and the rationale of their use appears sound from the above discussion. Certainly, more has been done to avoid future pancreatic involvement than if cholecystectomy alone were employed.

Chronic Recurring Pancreatitis.—Some of the failures in Group 1 continue on with recurring attacks of pancreatitis; these patients are relieved slightly by dieting and abstinence from alcohol, and present a group of seriously ill patients. In Group 2 are patients who apparently do not experience gall bladder disease per se, but whose attacks are typically pancreatic in type. The

attacks are manifested by upper abdominal pain, pain referred to the left shoulder, nausea, vomiting, fever, leucocytosis, and elevated serum amylase. Repetition of attacks of course is the common characteristic, and the sameness of symptoms is so pronounced that the patients soon learn to distinguish which of their abdominal attacks are actually pancreatic in type. Selective indigestion is common. There may be numerous small attacks, or an occasional severe one, but they have a tendency to increase in frequency and intensity as time passes. Vagueness is rather typical of the less severe attacks and because of this physicians will often associate this organic disease

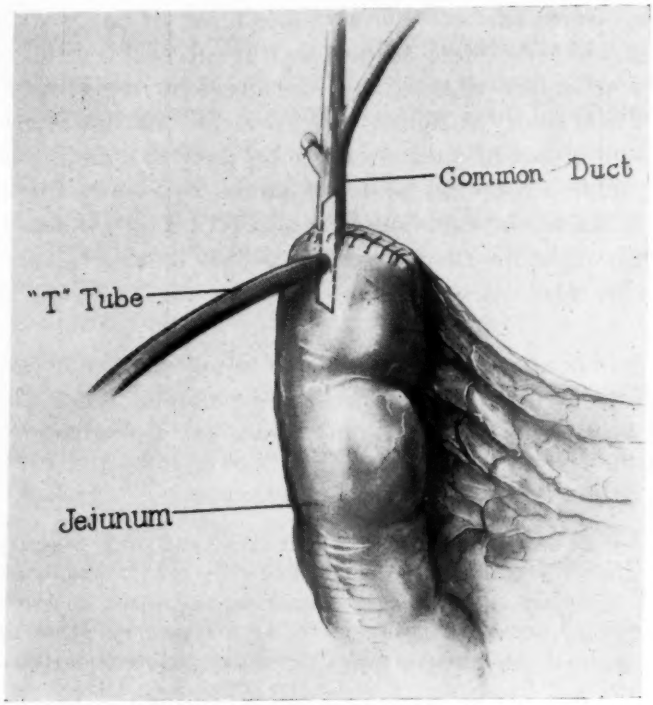

Fig. 1.—Sketch.

with psychogenic causes. Indeed the patients, frustrated by medical failures, often apparently magnify their troubles and become perhaps more apprehensive about their conditions than is compatible with the severity of the symptoms. The diagnosis is not difficult if the condition is borne in mind and serum amylase studies are done. Plain roentgenogram of the abdomen may show calcification in the pancreas.

Chronic recurring pancreatitis has been treated by biliary surgery as stated before. Many operators will not consider further treatment than the biliary surgery if recurrent attacks persist. Doubilet and Mulholland[2] have for many years advised cutting the sphincter of Oddi; this procedure relaxes the sphincter and prevents the flow of bile into the pancreatic duct. Consequently, if this etiological concept is sound, attacks of pancreatitis will not occur. They report large numbers of cases with good results, although there

have been some recurrences, particularly if the patient partakes heavily in alcoholic drinking. Sphincterotomy as employed by them can be performed by the indirect method of inserting a sphincterotome in the open common duct when the cutting is done blindly, or by duodenostomy when the cutting of the sphincter is done under direct vision. Following the suggestion of Greenfield,[3] we have employed an absolute shunting of bile away from the sphincter of Oddi by choledochojejunostomy en Roux Y. This is not a new procedure, as it has been employed by Allen,[4] Cole and associates,[5] and others in certain common duct strictures. Ostensibly, it requires division of the common duct near its distal end, which is ligated. The proximal end of the common duct is

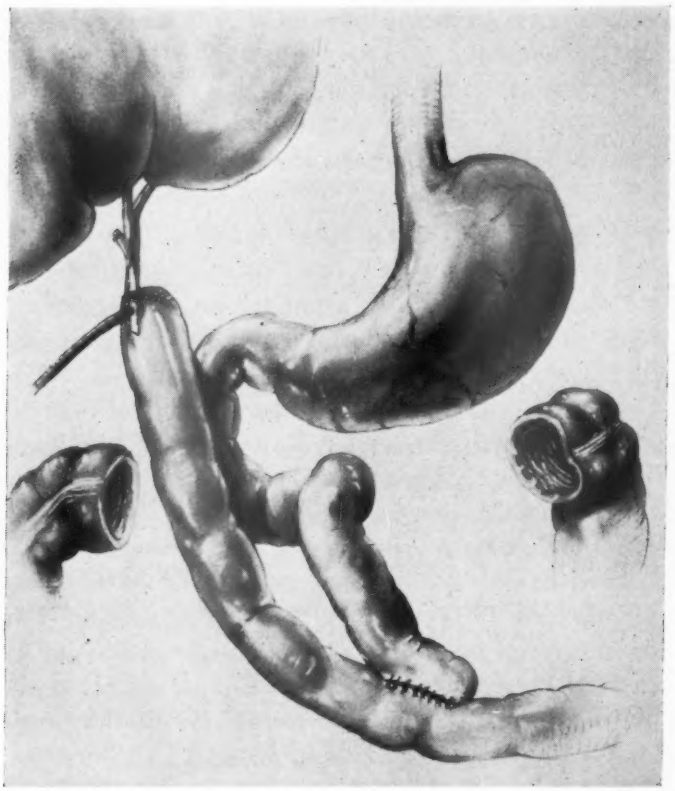

Fig. 2.—Sketch.

anastomosed to the lower end of the divided jejunum, after which jejunojejunostomy reunites the gastrointestinal tract. The sketches, Figs. 1 and 2, demonstrate the method. Table I contains the pertinent facts in the six cases. It will be noted that all patients have recovered without serious morbidity and have been relieved of their distressing attacks. Patient 4 experienced extravasation of bile in the abdominal wall which produced slough and eventually an incisional hernia. He has been free of pancreatic symptoms and so pleased with the result that he will not permit repair of the hernia. Patient 6 experienced partial duodenal obstruction for a period of two months postoperatively. This was undoubtedly due to an inflammatory reaction about

the duodenum, probably associated with the extensive infection in the pancreas at the time of operation. He has subsequently recovered, has had no pancreatic attacks, and has gained 22 pounds in weight. Patient 2 has experienced one slight attack of pancreatitis following a bout of heavy drinking. He is pleased with the relief afforded by operation. Patients 2, 3, 4, and 6 underwent biliary surgery prior to choledochojejunostomy without relief. The results in the six cases have been largely satisfactory.

TABLE I

PATIENT	AGE (YEARS)	DURATION	PREVIOUS SURGERY	OPERATION	COMPLICATION	FOLLOW-UP	RESULT
L. M.	34	6 yr.	None	Choledochojejunostomy March, 1948	Phlebothrombosis	1 yr.	No attacks; died auto accident 1 yr. 3 mo.
G. B.	41	2 yr.	Cholecystectomy August, 1948	Choledochojejunostomy December, 1948	None	2 yr., 1 mo.	One slight attack of pancreatitis after drinking bout, 7/18/49; well since that time
D. M.	42	3 yr. 5 mo.	Cholecystectomy; pancreatitis noted May, 1949	Choledochojejunostomy December, 1949	None	1 yr., 1 mo.	No attacks; gained 20 pounds
J. T.	60	18 yr. Intermittent	None	Cholecystectomy, choledochojejunostomy 3/27/50	Extravasation bile abdominal wall, incisional hernia	9 mo.	No attacks; feels better than he has for 20 yr.
R. B.	41	2 yr., 10 mo.	Exploratory laparotomy, 1947; acute pancreatitis	Cholecystectomy, choledochojejunostomy 5/3/50	None	8 mo.	No attacks; gained weight
C. B.	54	6 yr.	Cholecystectomy October, 1949	Choledochojejunostomy 9/11/50	Partial duodenal obstruction	4 mo.	No attacks; delighted with result

Choledochojejunostomy has been criticized because the operation is deemed too extensive and radical. The operation is tedious, requires about two and one-half to three hours, but is no more difficult or dangerous, for instance, than a high subtotal or total gastric resection and not so difficult or dangerous as pancreaticoduodenectomy or portacaval or splenorenal shunts. It is contended that the seriousness of the disease should not be underestimated, and that the relief is well worth the tedious work required. Two of our patients who have refused operation have gone on to severe malnutrition, anemia, cachexia, and drug addiction, to the extent that they are now hopeless gastrointestinal derelicts. Both are also suffering from marked pancreatic insufficiency with liver damage.

The small caliber of the normal common duct of course makes the anastomosis a tedious operation. There have been no strictures at the site of anastomosis. An ordinary T tube is inserted. The external limb of the T tube comes out of a small stab incision in the defunctioned jejunum about one inch distal to the anastomosis. In the first cases the T tube came out of a stab wound in the common duct a short distance above the anastomosis, but more drainage of bile was noted around the T tube in this position. The length of the defunctioned loop is approximately 18 inches, which assures, according to Pearse and associates,[6] the nonappearance of the dreaded cholangitis. It is believed that the presence of the anastomosis in the defunctioned loop aids in prevention of stricture at the site of anastomosis. This type of anastomosis has been used in two cases of common duct stricture and three cases where the bile duct had been injured in cancer surgery, and in nine pancreatic resections —a total of fourteen cases. No cholangitis or strictures have been observed. Some of the cases have been followed as long as three years.

The T tube is allowed to remain in place for a period of from two to three months. Patient 4 inadvertently removed the T tube on the thirteenth postoperative day without serious consequence. Perhaps these T tubes could safely be removed sooner.

Sympathectomy has been employed by Ray, Console, and others. Intra-abdominal denervation has been used; Ray and Console[7] favored thoracic sympathectomy. Sympathectomy has brought about relief of pain, but has not necessarily controlled the process in the diseased pancreas. One of Ray's cases developed an intra-abdominal abscess, presumably from the pancreas, after operation. Experimental work suggests that pancreatitis is not as easily produced in the experimental animal if sympathectomy is first employed. It is contended that the disease process will not be corrected by sympathectomy unless sympathectomy allows relaxation of the sphincter of Oddi. There is no proof that such relaxation follows. Gage and Floyd[1] stated that if morphine is given after relief is obtained by splanchnic block the relief is lost, which is indirect evidence that relaxation of the sphincter is not accomplished by sympathetic interruption. It is felt that sympathectomy offers relief from pain only and questionably for a temporary period of time. At the same time it may mask the abdominal findings if attacks of pancreatitis reappear, and for that reason be a dangerous method. However, sympathectomy and sphincterotomy are simpler procedures than choledochojejunostomy. It is hoped that the relief obtained by choledochojejunostomy will be permanent, where the relief in the other two procedures may be temporary.

"Burned Out" Pancreas.—This condition is easily recognized if once observed. The patient demonstrates marked weight loss and abdominal pain sometimes generalized and sometimes located in the upper left abdomen, but the pain is not as severe as in patients suffering from recurring pancreatitis. It is recognized that the "burned out" pancreas may follow many years of recurring pancreatitis. Mild diabetes and steatorrhea are usually present. Food intake is markedly restricted to a few simple foods which the patient

has learned to tolerate. One patient ate soup and milk only. Narcotic addiction, anemia, and avitaminosis are common. Liver damage of varying degree follows. Pathologically, marked fibrosis of the pancreas, calcification, a paucity of the islands of Langerhans, and pancreatic acini are observed Doubilet and Mulholland[8] have recently suggested that pancreatic calcification is the result of persistent pancreatic infection and that sphincterotomy should be performed in order to prevent the infection of the pancreas from further destroying active pancreatic tissue. The question arises, however, whether or not sphincterotomy or choledochojejunostomy can offer relief to the patients with burned out pancreas. Ostensibly, these patients have already undergone physiologic partial pancreatectomy and one wonders how the fibrotic state can be altered favorably. It follows that the best that could be hoped for would be to arrest further destruction of the pancreas.

There have been three cases of this type at Kennedy. One patient had carcinoma of the body of the pancreas, yet the nonmalignant pancreatic tissue both proximal and distal to the neoplasm demonstrated the marked fibrosis and scarcity of active pancreatic tissue. Partial pancreatectomy afforded slight palliative relief for a period of 6 months, but did not better the pancreatic insufficient state. The second case is that of a 20-year-old boy who had been subjected to attempted pancreaticoduodenectomy while in the Navy. Pyloric exclusion and gastrojejunostomy were done at the first stage. Marginal ulcer followed and gastric resection was necessary. After this latter operation, the patient refused any further operative treatment. Now, 5 years later, he weighs 80 pounds, is anemic (red blood count 2,200,000) and cachectic, demonstrates liver damage, and avitaminosis. Food intake is alarmingly low. Calcification of the pancreas is present and there is diabetes and steatorrhea. Pain has noticeably become less marked as he progressed from severe recurring pancreatic attacks until the present pancreatic insufficient state. Medical substitutive therapy failed and he refuses to accept the possible benefits of choledochojejunostomy or sympathectomy at this time. This cachectic narcotic addict appears to be doomed and death is imminent.

The third patient, a 41-year-old man, has suffered from what has been called recurring attacks of intestinal obstruction since 1944. The abdominal pains were severe, cramplike, but always accompanied by diarrhea. Exploratory operation with incidental appendectomy was done in 1944; no obstruction was found. When he was examined at Kennedy in October, 1949, the diagnosis was obvious. He complained of vague pain in the peri-umbilical region and left upper and lower quadrants, marked diarrhea (ten to twenty stools daily, with typical fatty appearance), calcification of the pancreas, serum amylase of 60 mg. per cent, and mild diabetes. Abdominal exploration revealed a small fibrotic, nodular, and partially calcified pancreas. Biopsies revealed marked fibrosis, paucity of active pancreatic tissue, and calcification (Fig. 3). Pancreatin and other medical measures were employed without relief. Left thoracic sympathectomy (ninth to twelfth thoracic vertebrae) was performed in March, 1950. An immediate change in the pain pattern

was noted. No left-sided abdominal pain is experienced and only slight pain in the right upper quadrant is noted. The patient feels encouraged, can eat slightly better, and has gained 5 pounds in weight, but steatorrhea and mild diabetes persist. He is still an invalid and cannot work. It is not likely that there will be further improvement. Apparently sympathectomy

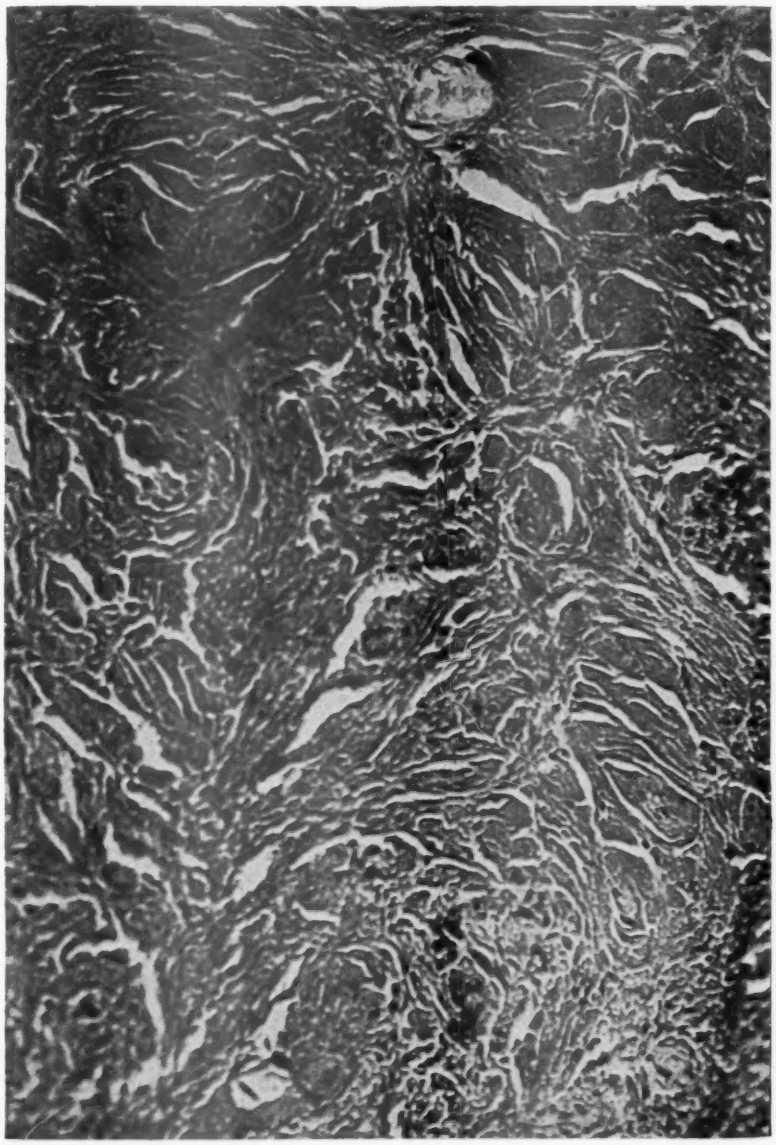

Fig. 3.—"Burned out" pancreas. Note marked fibrosis and paucity of active pancreatic tissue.

has helped the pain, but to date has not bettered the pathologic condition in the pancreas. Choledochojejunostomy is planned if further improvement is not noted. However, it is doubtful whether this procedure will help. Obviously then, burned out pancreas should not be allowed to appear. The pancreatic infection should be controlled by sphincterotomy or choledochojejunos-

tomy during the early phases of the disease. Sympathectomy has offered our patient improvement in the pain phase of his disease, but the result in this case cannot be compared to the favorable responses to surgical treatment for the chronic recurring pancreatic cases.

Cysts and Pseudocysts.—These tumefactions appear after trauma to the pancreas or as the result of infection. It is believed that the pancreatic juice is spilled at the time of injury, and as it spreads into the surrounding tissues, an inflammatory reaction follows which localizes by fibrosis. Absorption probably shrinks the inflammatory mass as the bodily defense prevents bacterial growth and consequently the patients remain asymptomatic permanently. If, however, absorption is not thorough or there is connection between the pancreatic duct and the involved area, then a cyst lined by typical epithelium or a pseudocyst may follow. These cysts enlarge, displace the colon toward the umbilicus and the stomach toward the xiphoid process and to the right. If the cyst is near the head of the pancreas, jaundice and duodenal obstruction are present. However, most of the reported cases locate the cystic process in the body or tail of the pancreas. Patients suffer pain, anorexia, vomiting, and gradually become malnourished to the point of cachexia. The pseudocysts are not epithelial-lined; the walls are formed by fibrous tissue. Both evoke the same symptomatology. They may become large and are subject to intermittent hemorrhages into the cystic fluid. The amylase content of the aspirated fluid is high. When they follow infection, the history is one of intermittent abdominal attacks that simulate intestinal obstruction, may demonstrate intermittent collections of ascitic fluid, following which a large cystic mass is formed in the upper abdomen, usually on the left side.

Operations that have been employed are marsupialization, cystenterostomy or cystgastrostomy, and excision.

Marsupialization is the simplest procedure and must be the method of choice if the patient is so desperately ill that more extensive surgery cannot be safely employed. The convalescence is lengthy and disagreeable, and recurrences sometimes occcur. The principle of marsupialization is one of external drainage, slough separation, and spontaneous closure of the portion of pancreatic duct which at some time was connected with the cyst. One cannot depend upon marsupialization to effect permanent cure.

Cystenterostomy or cystgastrostomy is simply the anastomosis of the cyst to the gut or stomach, which, in effect, is permanent internal drainage. Chodoff,[9] Gurwitz and Hurwitz,[10] and Poer[11] have employed the procedure with success. Apparently the continuous internal drainage effects cure. Also, the method may prevent bile under pressure or pancreatic juice under pressure in the pancreatic duct, and this may prove to be valuable if there is a tendency for recurrent pancreatitis.

At Kennedy Hospital this method has not been employed. If the occasion arises, however, cystojejunostomy en Roux Y would appear to be the procedure of choice. It requires transection of the jejunum, anastomosis of the distal jejunum to the cyst, and jejunojejunostomy at a level about 18 inches

below the cystojejunostomy. Although no serious sequellae have been reported by anastomosis to the bowel in continuity, certainly a defunctioned loop of jejunum should more definitely assure safety.

Excision of the cyst or pseudocyst along with partial pancreatectomy should effect cure in all cases. Most writers on the subject admit that excision would be preferable, but that the technical dangers of excision are such that one of the other two methods is most often employed. As stated previously, the greater number of these cysts occur on the left side and their

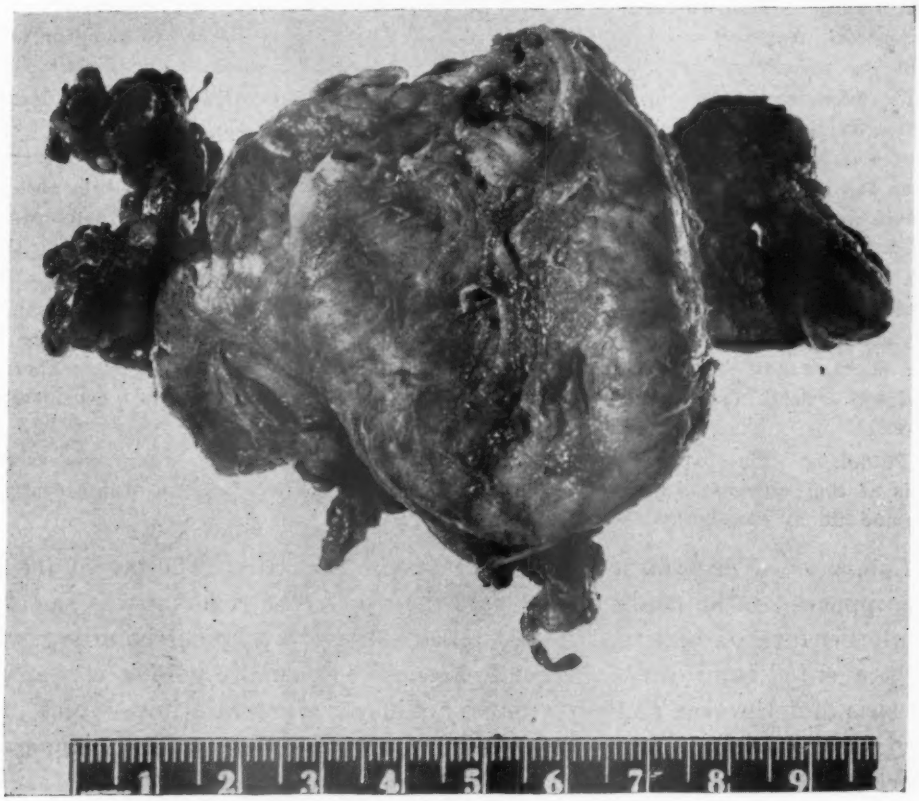

Fig. 4.—Pseudocyst pancreas removed at operation.

size often suggests that the origin of the cyst may be in a lengthy segment of pancreas and therefore excision would mean injury to the portal vein, mesenteric vessels, or the hepatic artery. There is no question that if the attempted excision should cause injury to these major vessels, a fatal outcome would ensue.

However, the two cases to be cited demonstrate the fact that the location of the point of origin in the pancreas occurred in the tail of the gland. When first observed at laparotomy, the immensity of the cystic mass suggested simpler procedures. Aspiration of the cyst contents allowed careful examination of the important structures, and that examination clearly dictated excision without too much difficulty. In each instance it was necessary to in-

sert the finger in the cyst cavity and palpably explore all interstices so that safe maneuvering could be predicted. Marsupialization or cystenterostomy can be performed if the aspiration and examination fail to establish the safety of excision.

CASE REPORTS

CASE 1.—A 32-year-old man was struck in the left abdomen with a plank approximately 2 years before admission. Left upper quadrant pain persisted, with definite exacerbations so intense that he was unable to work. The severe pain lasted about 24 hours during the exacerbations, and then remained constant and dull until the next bout. During attacks the patient noticed swelling in the left upper abdomen. Occasionally the pain was referred to the left shoulder. Appetite was fair, but he noticed that food intake seemed to bring on attack. Weight loss was 30 pounds. There was left upper quadrant tenderness and rigidity, and a palpable mass in the left upper quadrant. Roentgenogram revealed an elevated left diaphragm. There was no colon or stomach displacement. White blood count was 14,000. Serum amylase was 326 mg. per cent. There was no diabetes. Operation revealed a large cystic mass between the pancreas and left kidney. The cyst contained about 1,200 c.c. of brownish fluid. The fluid demonstrated an amylase content of 611 mg. per cent. Cyst, tail of pancreas, and spleen were removed en bloc. It was noted that the left renal vein was injured during the removal. This was successfully controlled by suture, but fear of postoperative hemorrhage prompted the removal of left kidney. A drain was placed to the stump of the pancreas. There was no pancreatic fistula. The patient was discharged from the hospital on the fourteenth postoperative day. At follow-up examination one year, two weeks after operation, weight was normal, appetite was good, and there was no pain. The patient considers himself well.

Pathology.—The pathologic report was a pseudocyst pancreas. There was extensive fibrosis of the pancreas with chronic inflammation near the site of origin of the cyst. The spleen and kidney were normal (Fig. 4).

Comment.—The cyst was located below the pancreas. The tail of the pancreas appeared to be floating on top of the cyst. The removal was somewhat difficult because of this posterior position. Better technical handling would have prevented the injury of the renal vein. The small opening was sutured with ease, but the fear of the digestive action of pancreatic juice which might collect in the area prompted nephrectomy to prevent possible postoperative hemorrhage.

CASE 2.—This 58-year-old white man (Fig. 5) had been an alcoholic for many years. For the past four years he has had intermittent swelling of the abdomen and feet. For one year, he had loss of appetite, weight loss of 20 pounds, and intermittent abdominal pain and swelling. There was no injury. He was emaciated, with distended abdomen and ascites. Serum amylase was 79 mg. per cent, red blood count 3,750,000, white blood count 15,400, serum protein 4.3 Gm., albumin 1.4, globulin 2.9, serum bilirubin 3 mg. per cent. Roentgenograms revealed a typical upward displacement of the stomach and downward displacement of the transverse colon. After paracentesis of 800 c.c. of fluid, a large cystic mass was felt in the left upper quadrant. Hypoproteinemia was corrected. On Nov. 24, 1950, operation revealed a large cyst; 3,600 c.c. of reddish-brown fluid were aspirated. The cyst, spleen, and tail of the pancreas were resected without too much difficulty (Fig. 6). The cyst arose in the tail of the pancreas.

Pathology.—The pathologic report was pseudocyst pancreas, with fibrosis of pancreas in area adjacent to cyst. At follow-up examination Jan. 15, 1951, the patient had gained 12 pounds and demonstrated no symptoms.

Comment.—This case is one of cystic collection of fluid around the tail of the pancreas, following many years of abdominal attacks suggesting pancreati-

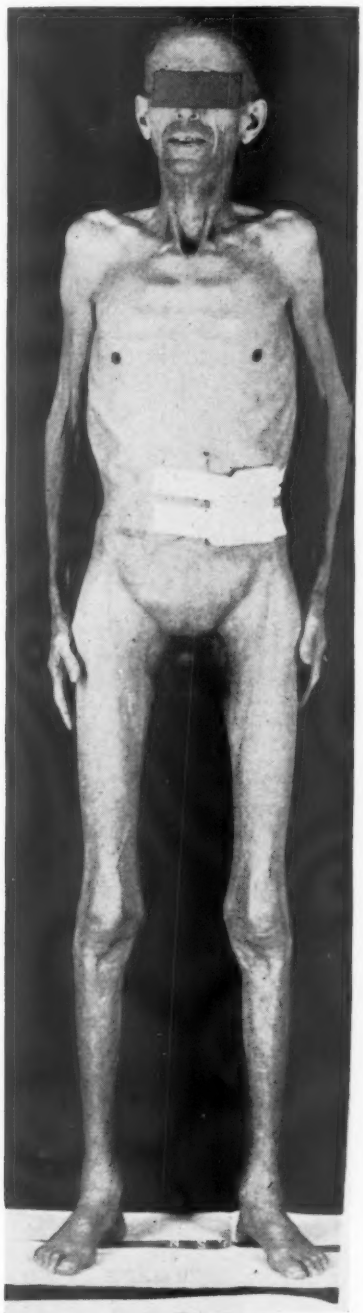

Fig. 5.—Denotes marked cachexia in patient with pancreatic pseudocyst.

tis with ascites. At operation the large cyst presented a picture of involvement of a large area of pancreas. After aspiration, it was obvious that only a small portion of the pancreas was involved, and the cyst-bearing area was

removed with great simplicity. The mesocolic vessels were retracted from the cyst wall with ease. No other major blood vessels were involved in cystic mass. Permanent cure is expected.

Fig. 6.—Photograph of opened pseudocyst. Arrow points to connection of cyst with the tail of the pancreas.

SUMMARY

1. Operative therapy has proved to be satisfactory in the treatment of chronic pancreatitis. Biliary surgery with common drainage effects relief for an unknown number of patients.

2. Choledochojejunostomy en Roux Y affords relief in the recurring pancreatitis group. The results in six cases are briefly recorded.

3. Patients with "burned out" pancreas should probably be subjected to sphincterotomy or choledochojejunostomy early in order to prevent destruction of pancreatic tissue. Sympathectomy has been helpful in one reported case.

4. Excision of cysts is the operation of choice if technically feasible. Two cases are reported. Cystenterostomy or marsupialization may be employed if excision is not possible.

REFERENCES

1. Gage, Mims, and Floyd, Jack B.: The Treatment of Acute Pancreatitis, With Discussion of Mechanism of Production, Clinical Manifestations and Diagnosis and Report of Four Cases, Tr. South. S. A. **59**: 415-442, 1948.
2. Doubilet, H., and Mulholland, J. H.: Recurrent Acute Pancreatitis: Observations on Etiology and Surgical Treatment, Ann. Surg. **128**: 609-638, 1948.
3. Bowers, R. F., and Greenfield, Jack. Choledochojejunostomy—Its Role in the Treatment of Chronic Pancreatitis. In press.
4. Allen, Arthur W.: A Method of Re-establishing Continuity Between the Bile Ducts and the Gastro-Intestinal Tract, Ann. Surg. **121**: 412-424, 1945.
5. Cole, Warren H., Reynolds, John T., and Ireneus, Carl, Jr.: Strictures of the Common Duct, Ann. Surg. **128**: 332-347, 1948.
6. Pearse, Herman E., Radakovich, Michael, and Cogbill, Charles L.: An Experimental Study of Antiperistaltic Jejunal Loops, Ann. Surg. **129**: 57-64, 1949.
7. Ray, Bronson S., and Console, A. Dale: The Relief of Pain in Chronic (Calcareous) Pancreatitis by Sympathectomy, Surg., Gynec. & Obst. **89**: 1-8, 1949.
8. Doubilet, H., and Mulholland, J. H.: Surgical Treatment of Calcification of the Pancreas, Ann. Surg. **132**: 786-797, 1950.
9. Chodoff, Richard J.: Pancreatic Pseudocysts: Report of a Case Treated by Cystogastrostomy, Ann. Surg. **128**: 981-986, 1948.
10. Gurwitz, Jack, and Hurwitz, Alfred: Treatment of Pancreatic Cysts, Ann. Surg. **128**: 976-980, 1948.
11. Poer, D. Henry: Personal communication.

(See Discussion on page 145)

A CLINICAL STUDY OF THE EFFECT OF VAGOTOMY ON RECURRENT ACUTE PANCREATITIS

ROBERT S. MCCLEERY, M.D., JOHN E. KESTERSON, M.D., AND WILLIAM R. SCHAFFARZICK, M.D., NASHVILLE, TENN.

(From the Surgical Service, Thayer Veterans Administration Hospital, and the Department of Surgery, Vanderbilt University School of Medicine)

ALTHOUGH the etiology of acute pancreatitis has long been widely investigated, there is yet no general agreement upon a single major causative mechanism. As a consequence, the therapeutic regimens advocated for the recurrent attacks of this serious entity have run the gamut from palliative reapplication of conservative measures through vigorous surgical exercises of many types. The idea of the necessary association of cholelithiasis, common duct stone, blockage of the ampulla of Vater, and reflux of bile into the pancreatic ducts has long, and unfortunately, influenced the surgical approach to the alleviation of these recurrent attacks. Doubilet and Mulholland,[1] although still believing in the "common channel" and reflux theory, have pioneered the new clinical attack of sphincterotomy, based on the theory that ampullary muscle spasm is the fundamental abnormality. However, there is sufficient clinical and experimental evidence to suggest that occlusion of the pancreatic duct alone, perhaps by sphincter spasm, is capable of producing all the pathologic and clinical features of the disease. It is our purpose here to suggest that recurrent acute pancreatitis may be of psychogenic origin. We propose also to review the extant experimental data and to report the results of vagotomy in 11 patients, which lend validity to this concept.

The personality and emotional background observed in these patients are similar qualitatively, though more striking quantitatively, to the so-called "ulcer" type. The association of emotional disturbance with the onset of pain is commonly elicitable from the patient. If vagal discharge is accompanied by marked increase in pancreatic secretion, associated with spasm of the ductal opening, then pancreatic necrosis and inflammation might supervene.* The encouraging results obtained by testing this theory in an experimental study[2] led to the application of vagotomy to patients with a long history of recurrent acute pancreatitis.

The literature contains sufficient evidence justifiably to inter, once and for all, the idea promulgated first by Opie,[3] in 1901, that infection and stone in the biliary system is the major causative factor of acute pancreatitis. The reviews of Ravdin and Johnston,[4] and Lium and Maddock[5] are excellent sources of facts disproving the theory of "common-channel," blockage by stone, and reflux of bile as the preponderant mechanism in the causation of this disease. This is reviewed briefly here because this very hardy and tenacious misconception has led to an erroneous concentration of surgical approach on the biliary system. The refutation comes from 4 sources: studies of autopsies, reports of relatively large

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percentages of cases demonstrated to have neither cholecystitis nor cholelithiasis, failure to prevent recurrences following removal of the gall bladder, and, finally, from experimental studies.

Mann and Giordano,[6] in studying the ductal system in 200 autopsies, believed that a stone could produce a common channel in only 3.5 per cent of the cases. In the autopsy of 11 who had acute pancreatitis, they noted that in none could a common passage have been produced by obstruction of the ampulla. In a similar study of 250 autopsies, Rienhoff and Pickrell[7] concluded that such an occurrence was possible in 17 per cent. Edmondson and associates,[8] in 62 autopsies of patients with pancreatitis, found no obstruction to the pancreatic or common bile ducts. Their histologic examination did reveal focal areas of lobular pancreatic destruction in widely separated areas.

The latter authors also noted that only 20 per cent of their patients had stones in the gall bladder, while none had common duct stones. Gambill and associates[9] found 29 of 56 patients to have no disease of the biliary tract. In comparing the two groups, they concluded that the anatomic and histopathologic features, clinical picture, and sequelae were similar, regardless of the presence or absence of cholecystitis and cholelithiasis. Muether and Knight[10] found that 39 per cent of 58 patients had jaundice with attacks of pancreatitis, independent of any gall bladder disease.

Northman[11] presented a series of 15 patients, in 7 of whom the gall bladder had been previously removed without relief of symptoms. In 5 of the 8 other cases, cholecystograms revealed normal function. The study of the cases herein reported offers confirmation of all the preceding opinions.

It has been indisputably proved that experimental injections of bile into the pancreatic ducts will cause pancreatitis. In this regard the work of Archibald[12] is frequently quoted. He reported injection pressures up to 500 mm. of mercury. Lewis and Wangensteen[13] similarly produced pancreatitis and reported the use of high injection pressures of 400 to 500 mm. of mercury. Mann and Giordano[6] stated that physiologic pressures do not exceed 375 mm. of bile. When they made such injections within physiologic limits pancreatitis was not produced. Although in human being we have observed abnormal sphincter opening pressures of 400 to 600 mm. of bile, none has approached the extremely high pressure used by Archibald.

The attractiveness of the necessity of a common channel depends largely on the theory that the presence of bile is necessary for the activation of trypsin. Obstruction of the pancreatic duct alone would be sufficient if other activators of trypsin were present. Babkin[14] has shown that calcium salts, tissue extracts, and bacterial products will activate trypsin. Thus, if pancreatic enzymes pass into the periacinar connective tissues, by rupture of the ducts, then they could be activated by calcium salts. Rich and Duff[15] were able to produce the disease by retrograde ductal injection of trypsin, while heat-inactivated trypsin was benign. The same workers showed that when as little as 2 c.c. of India ink were so injected, several ducts were ruptured and ink particles were extruded into the perilobular connective tissue.

Pancreatitis similar in every way to the clinical type, except for the gangrenous changes, can be produced by ligation of the pancreatic duct alone.

Working with cats, Lium and Maddock[5] were able to demonstrate conclusively that such ligation in the presence of an actively secreting gland resulted in pancreatitis and fat necrosis. Our own experimental results in dogs verified their statements.[2] In neither instance was there a possibility of bile reflux. Wangensteen and associates[16] produced pancreatitis in cats by ligation of the ampulla of Vater. This work has been quoted as evidence that the attendant reflux of bile was the cause of the resulting pancreatitis. It is open to the criticism that a control series was not done in which the pancreatic duct alone was ligated.

Since experimental pancreatitis can be produced by obstruction of the pancreatic duct alone in the presence of an actively secreting gland, it is of importance to determine if vagus stimulation can produce both of these conditions. Lium and Maddock[5] reported the development of an acute pancreatitis in cats when the vagus nerves were repeatedly stimulated with the pancreatic ducts ligated. Mellanby,[17] Routley and co-workers,[18] and Kuntz and Richins[19] observed that such stimulation produces an increased secretion of pancreatic juice, very high in enzyme content. Selye[20] described the discharge of zymogen granules from the acini during the alarm reaction to various types of stress, and stated that pancreatic necrosis may follow.

Since the work of Bayliss and Starling[21] it has been widely observed that secretin injections cause a copious secretion of a low-enzyme, watery fluid. Kuntz and Richins[19] have demonstrated that splanchnic sympathetic nerve stimulation results in a similar type of secretion. Thomas and Crider,[22] on the other hand, have shown that the presence of peptones and hydrochloric acid in the intestinal tract results in a secretion similar to that from vagal stimulation. The response to both stimuli can be abolished for some time by vagotomy. They believe that the role of vagus control of pancreatic secretion is that of a tonus mechanism serving to augment or to inhibit local reflexes. Routley and associates[18] agree with this concept.

Although Bockus[23] feels that the weight of opinion favors the view that both the sympathetic and parasympathetic nerves carry inhibitor and motor impulses to the ampulla, there is evidence to indicate that parasympathetic stimulation alone can produce spasm. Wener and associates[24] produced acute pancreatic necrosis in 8 of 48 dogs given daily injections of Mecholyl. In some, hemorrhagic changes also occurred. They postulated that this might be the result of ductal spasm associated with increased enzymatic secretion. McGowan and co-workers[25] reported a marked increase in bile pressure after morphine sulfate had been given and that this pressure could be relieved by glyceryl trinitrate. Elman[26] also noted relief from an attack of acute pancreatitis by the use of the same drug. Von Anrep[27] cannulated the pancreatic duct and found that early during stimulation of the vagus there was no secretion of juice and that the pancreas increased markedly in size. He believed this is to be the result of increased secretion combined with spasm of the pancreatic duct.

If activity of the vagus nerves can produce temporary occlusion of the pancreatic duct outlet and also a high enzymatic secretion, then such occurrence with psychic, emotional, and other central inciting causes of vagal excitation (for example, hypoglycemia) would have real meaning in relation to the etiology of the disease in human beings. Pavlov[28] noted, by his sham feeding method,

that pancreatic secretion increased with this psychic stimulation. He believed the vagus nerves to be the mediator of this stimulus. Routley, Mann, and associates[18] described an increase of pancreatic secretion from experimental fistulas as a result of many parasympathetic stimulators (for example, pilocarpine, Mecholyl, hypoglycemia, and psychic excitation). Vagotomy resulted in a marked diminution of response only to hypoglycemia and psychic stimulation. Doubilet and Mulholland[29] recorded a marked increase of sphincter tone as a result of pain and emotional upset. This change was reversible when the patient was reassured. Case 11 of our series gives striking corroboration to these experimental facts.

The pancreatitis produced by stimulation of the gland by feedings, with the ducts ligated, is accompanied by a great elevation of the blood amylase.[2] With vagotomy, we found a marked decrease in the amount of pancreatic necrosis, and hemorrhage, and also in the blood amylase response to the same experimental insult. Popper and co-workers[30] were unable to produce pancreatitis with necrosis by injections of secretin, even though the pancreatic ducts were ligated.

Lium and Maddock[5] expressed very well a theory of pathogenesis with which we heartily agree. They believe that edema of the pancreas under normal conditions is a temporary stage associated with vagal stimulation. This normal reflex when pushed beyond physiologic limits could provide complete obstruction to an increased, high enzyme-containing secretion. We feel that emotional stimulation of vagus activity may be the major inciting cause to such a vicious circle. If secretion was high and spastic obstruction incomplete—or if secretion was low with complete obstruction—then a short attack of pancreatic edema might supervene. If complete obstruction and high secretory activity occurred simultaneously then pancreatic necrosis and hemorrhage would be the result. In a small percentage of cases, the presence of stones or cholecystitis might render the ductal system more sensitive and lead thus indirectly to the onset of spasm and pancreatitis. Widespread clinical experience indicates this association is of minor import in the over-all incidence of human pancreatitis.

Rienhoff and Baker[31] have reported a patient showing marked improvement following transthoracic sympathectomy and vagotomy. Richman and Colp[32, 33] performed partial gastrectomy on 3 patients. Complimentary vagotomy was added in 2 of these. They seemed to feel the improvement resulted principally from decreased secretin production incident to diversion of chyme from the duodenum. More recently Rack and Elkins[34] reported 2 patients treated by subdiaphragmatic vagotomy, neither of whom was benefited. The former reports are subject to the criticism that the multiple procedures do not permit the improvement to be ascribed to either measure alone. Our clinical experience with 11 patients, followed 6 to 22 months, leads us to believe that vagotomy produced great improvement in all cases.

METHODS

Vagotomy.—The usual subdiaphragmatic procedure was followed. The technical difficulties varied only slightly from those encountered when the operation is performed for duodenal ulcer. It is well to re-emphasize that the large

posterior nerve to the celiac plexus may leave the esophageal wall in the mediastinum. Unless a diligent search is made in the areolar tissue, posterior and medial to the esophagus, this most important branch may be completely missed.

Gastroenterostomy.—A dependent, greater curvature stoma[35] was formed when this procedure was added to vagotomy.

Cholangiograms.—Ten minutes following an intravenous injection of morphine sulfate (0.01 Gm.), 20 c.c. of 35 per cent Diodrast were injected into the common duct during the operative procedure.

Serum Amylase.—The Somogyi method was used and 200 mg. per cent was considered the upper limit of normal.

Hollander Test.—A gastric tube was inserted and an overnight specimen was obtained for volume of secretion and total and free acid. Fasting gastric samples and blood sugar were obtained. Fifteen units of regular insulin were then injected intravenously, after which these determinations were repeated at ½, 1, 1½, and 2 hours.

GENERAL REVIEW OF CASE HISTORIES (TABLE I)

Duration of Disease.—Ten of the 11 patients gave a history of similar attacks for 2 to 10 years. The patient with the worst case of the group had a history of only one year with a rapidly downhill course, manifested by pancreatic calcification, insufficiency, and one episode of subphrenic abscess formation.

Frequency and Severity of Attacks.—All had recurrent attacks at least every 2 to 3 months, lasting from several days to 2 weeks. The disease was progressive and almost all, in the few weeks before vagotomy, were having daily to weekly episodes. Five of the 11 had come to the point of drug addiction from the almost constant nature of their pain.

Weight Loss.—The weight loss had ranged from 11 to 90 pounds and most commonly was in the area of 20 to 30 pounds.

Emotional Background.—In all a careful psychiatric study revealed definite personality and emotional inadequacies.

Alcohol Intake.—A further indication of the general mental instability of this group was the fact that 9 of them were frequent partakers of alcoholic beverages. Five of the 11 were heavy drinkers. Many had sufficient insight to believe their drinking was secondary to their personal difficulties, and that excessive intake seemed to precipitate attacks of pain.

Jaundice.—Six of the patients had had jaundice, lasting several days at least, at one or more times in their past history. This had occurred during one of the typical attacks of pain.

Cholecystograms.—Two of the group had a previous cholecystectomy. Nine of the 11 had cholecystograms, all of which were normal, except for one which showed stones.

Serum Amylase.—Ten of the 11 had been found to have an elevated amylase in this hospital, on at least one occasion.

CASE 1.—N. C., a 46-year-old veteran, was admitted on Sept. 14, 1948, with a 4-month history of recurrent pain in the left upper quadrant, which radiated into the back and was

accompanied by anorexia, nausea, and vomiting. The patient had lost 20 pounds in the 4 months, and had also noted an increased number of stools—3 to 6 a day. This was well controlled later by pancreatin administration. Examination revealed a small man with marked left upper quadrant abdominal tenderness. A gastrointestinal series revealed a mass posterior to the stomach and calcification was seen in the soft tissues in the region of the pancreatic body and tail. On Sept. 21, 1948, severe abdominal pain, nausea and vomiting, fever and tachycardia began. The serum amylase was increased. A laparotomy was done, at which time a large, multiloculated pancreatic abscess extending into the left subphrenic space was drained. Improvement followed operation but abdominal pain continued. On Nov. 22, 1948, fever and glycosuria developed, and an oral glucose tolerance test showed a decreased tolerance to glucose. The patient was transferred to the Medical Service where diabetes was controlled with insulin and diet.

TABLE I

CASE NO. AND AGE	DURATION OF DISEASE	FREQUENCY OF ATTACKS	WT. LOSS IN POUNDS	EMOTIONAL BACKGROUND	ALCOHOL INTAKE	HISTORY OF JAUNDICE	CHOLECYSTO-GRAM	SERUM AMYLASE ELEVATED = +- NOT " = —		REMARKS
1. N.C. 46	12 MOS.	1 MONTH	40	INADEQUATE PERSONALITY	MODERATE	NO	NORMAL	+		PANCREATIC CYST DRAINED 8 MOS. PRIOR TO VAGOTOMY.
2. L.H. 33	6 YRS.	2-3 MONTHS	30	INADEQUATE PERSONALITY	MODERATE	YES	NORMAL	+		ADMITTED WITH ACUTE HEMORRHAGIC PANCREATITIS. DEVELOPED PHLEBOTHROMBOSIS. Ca = 8
3. W.C. 36	4 YRS.	WEEKLY	22	MARITAL STRESS	HEAVY	NO	NORMAL	—		BILATERAL SYMPATHECTOMY AND SPLANCHNICECTOMY
4. E.H. 31	10 YRS.	WEEKLY	16	INADEQUATE PSYCHOPATH MARITAL STRESS	HEAVY	NO	NORMAL	+		LAPAROTOMY IN ARMY IN 1943 REVEALED PANCREATITIS.
5. C.B. 34	5 YRS.	WEEKLY	11	INADEQUATE PERSONALITY	HEAVY	NO	NORMAL	+		2 PREVIOUS LAPAROTOMIES - 1945 AND 1949 - REVEALED PANCREATITIS. BIOPSY
6. R.H. 33	10 YRS.	2-3 MONTHS	90	INADEQUATE PERSONALITY	MODERATE	YES	NORMAL	+		PROSTIGMINE INDUCED SEVERE PAIN AND AMYLASE ROSE FROM 174 TO 388 MG. %
7. T.J. 35	4 YRS.	2 MONTHS	25	TENSE, NERVOUS, INSECURE	HEAVY	YES	G.B. REMOVED 2 ½ MOS. PREVIOUSLY	+		CHOLECYSTECTOMY FOR CHOLELITHIASIS 2 ½ MOS. PRIOR TO VAGOTOMY RETURNED WITH "SAME PAIN AS BEFORE" IN ATTACK OF PANCREATITIS
8. R.S. 34	2 YRS.	2-3 MONTHS	17	TENSE, NERVOUS, TAXI DRIVER	MODERATE	YES	NOT DONE - STONES AT OPERATION	+		COMMON DUCT NORMAL - NO STONES AMYLASE 534 MG. %
9. L.P. 49	"ULCER" 18 YRS. WORSE - 4 YRS.	2 MONTHS	25	TENSE, NERVOUS ANXIOUS	NONE FOR 4 YEARS	YES	NORMAL	+		DUODENAL ULCER ANTERIOR WALL OF DUODENUM.
10. M.D. 43	5 YRS.	3 MONTHS	21	INADEQUATE, NERVOUS	HEAVY	NO	POOR FUNCTION NO STONES	+		TRANSVERSE EPIGASTRIC MASS FELT ON ADMISSION
11. M.M. 39	8 YRS.	1 MONTH	30	INADEQUATE, DEPENDENT HYPOCHONDRIAC	NONE	YES	G.B. REMOVED 3 YRS. PREVIOUSLY	+		CHOLECYSTECTOMY - 1947, SAME PAIN RECURRED. PANCREATIC ABSCESS DRAINED - 1948. CYST REMOVAL ATTEMPTED - 1949.

The second admission was on April 20, 1949. The patient had continued to lose weight (a total of 40 pounds) and 2 months prior to admission, he had again developed severe left upper quadrant pain which radiated into the back. This subsided in 3 days, but recurred 10 days before admission, and was associated with fever, nausea, and vomiting. Examination revealed the old incision to be well healed; there was left upper quadrant tenderness. The patient improved on large doses of tincture of belladonna, and on May 16, 1949, a laparotomy was carried out, at which time the body and head of the pancreas were found to be enlarged, irregular, and firm. The gall bladder and common duct were normal. Subdiaphragmatic vagotomy was performed. Following operation the patient did extremely well, being free of pain and gaining 20 pounds in 2 months.

The patient returned to the hospital on March 25, 1950, complaining of epigastric fullness. A gastrointestinal series showed marked retention at 7½ hours, and urecholine was given with moderate improvement. Atony continued and on May 8, 1950, a gastroenterostomy was done. At the present time the patient is free of pain but has required further hospitalization

only because of two attacks of asthma, with severe cough and bronchitis. The patient returned on Nov. 9, 1950, complaining of 4 to 10 frothy bowel movements per day. The steatorrhea disappeared with pancreatin administration. The glycosuria has disappeared and no insulin has been required for the past year.

This patient had had one of the severest forms of pancreatitis, with one episode of a subphrenic cyst-abscess. The diabetes seemed improved by vagotomy and no insulin is now required. Severe asthma and bronchitis, with pancreatic insufficiency, keep the patient from full health, but there has been no further evidence of acute pancreatitis in the 22 postoperative months and he now is 20 pounds above the preoperative weight.

CASE 2.—L. H., a 38-year-old farmer, was first admitted to the hospital on April 2, 1946, with a 3-year history of attacks of epigastric pain associated with vomiting. The attacks of pain occurred every 2 or 3 months, lasted from 1 to 14 days, were unassociated with food intake, were not relieved by food or alkali, but were relieved by narcotics. The patient also noted marked nervousness and insomnia, and had been discharged from the Army because of these symptoms. Examination of the abdomen revealed slight tenderness to deep palpation in the epigastrium. Chest roentgenograms and gastrointestinal series were negative. A diagnosis of gastric neurosis was made and the patient was discharged on a bland diet.

The second admission was on Aug. 6, 1948, at which time the complaints were the same. The episodes of pain had continued, becoming more frequent, and could be relieved only by morphine. Physical examination was essentially the same as on the first admission. The serum amylase was not elevated and the fasting blood sugar was 85 mg. per cent. Examination of the gall bladder revealed normal function, and a flat plate of the abdomen did not reveal pancreatic calcification. It was felt that this patient was suffering from recurrent attacks of acute pancreatitis. The patient improved gradually and was discharged on Sept. 11, 1948.

The patient was admitted for the third time on April 19, 1949, complaining of severe epigastric pain, nausea, and vomiting of 5 days' duration. Examination revealed an icteric, desperately ill man, whose lips and nail beds were dusky, and whose skin also showed cyanosis. Temperature was 99.8° F., pulse was 140 and was thready and weak, blood pressure 55/40, respirations 22, and white blood count 16,500. An emergency serum amylase was 192. On the second hospital day the nonprotein nitrogen was 89, the icterus index was 36, and the calcium was 8 mg. per cent. The patient, treated with whole blood transfusions, oxygen, adrenal cortical extract, calcium gluconate, and gastric suction, showed slow improvement. A gastrointestinal series on April 20, 1949, showed hypermotility of the second portion of the duodenum with puddling of barium, and a repeat examination on April 24, 1949, revealed duodenal irritability and anterior displacement of the second portion of the duodenum on the lateral view. Serum amylase values ranged from 56 to 192. Venous thrombosis which developed in the left leg subsided rapidly under heparin therapy.

On June 1, 1949, a laparotomy revealed that the pancreas was fibrotic, irregular, and hard. The gall bladder, and cystic and common ducts were normal. A cholangiogram, made through the cystic duct stump, revealed no pancreatic duct reflux. A cholecystectomy and subdiaphragmatic vagotomy were done. The common duct was not drained.

Postoperatively the patient noted a cessation of the epigastric pain, a return of appetite, and soon gained 10 pounds. Returning for follow-up studies 4 months later, he complained of some fullness and nervousness. A gastrointestinal series revealed 30 per cent retention. This feeling of fullness has subsided and at the present time he states that he has had no pain in the epigastrium. He has gained 30 pounds since the operation.

This case illustrates how often the diagnosis of pancreatitis is overlooked, especially when elevation of the blood amylase is not observed. The patient had a most severe episode of acute hemorrhagic pancreatitis after 6 years of

recurrent attacks. No further pancreatitis has occurred in the 21 months following vagotomy.

CASE 7.—T. J., a 35-year-old veteran, was first admitted on Dec. 14, 1949, complaining of pain across the upper abdomen for 4 years, postprandial fulness, and alternate constipation and diarrhea. Eight months before admission the patient had been hospitalized elsewhere because of severe epigastric pain, hematemesis, and icterus, and had been told that the serum amylase at that time was elevated. The patient now had slight tenderness in the area of the umbilicus. Cholecystography revealed several non-opaque stones, and on Dec. 21, 1949, a cholecystectomy was performed. The postoperative course was uneventful and the patient was discharged on Jan. 12, 1950.

The patient returned to this hospital on Feb. 23, 1950, complaining of a recurrence of the upper abdominal pain associated with nausea and vomiting. He stated that for one week following discharge he had been free of pain but that he had experienced 3 severe episodes of pain in the 5 weeks prior to admission. Examination revealed moderate icterus, and epigastric, right upper quadrant, and left upper quadrant tenderness. The serum amylase was 1,233, white blood count, 13,900, and icterus index, 44. The patient was treated conservatively by gastric suction, parenteral fluids, and penicillin and showed rapid improvement. The serum amylase fell to 279 by the fourth hospital day, and the patient became free of pain (Fig. 1).

On the eleventh hospital day (March 6, 1950) the patient began again to have severe epigastric pain, nausea, and vomiting. Temperature rose to 104° F. and pulse to 110. Amylase, early in this attack of pain, rose to 855 mg. per cent. A laparotomy on March 8, 1950, revealed a large, thick, edematous pancreas, which was twice its normal size. There was marked edema of the entire peripancreatic area and retroperitoneal areolar tissues. Several areas of old calcification were present in the omentum and on the posterior peritoneum. Edema fluid aspirated from the areolar tissues, in the retroperitoneal area, yielded an amylase value of 9,710 mg. per cent. The common duct was small and thin-walled, contained no stones, and a probe was easily passed into the hepatic ducts and duodenum. Vagotomy was performed.

Despite the fact that exploration was carried out during the acute phase of pancreatitis, the postoperative course was exceedingly smooth. Abdominal pain ceased by the first postoperative day and has not since recurred. Amylase postoperatively fell rapidly to normal (Fig. 1). The patient has returned for follow-up studies at 3, 6, and 9 months and states he has had no pain. He works daily and has gained 22 pounds.

This patient had not been relieved by previous cholecystectomy. It is of interest to note that a recurrent acute attack occurred in the hospital while he was on conservative treatment. Vagotomy was performed in the acute phase with a retroperitoneal fluid amylase of 9,710 mg. per cent. The attack subsided immediately after vagotomy, as manifested by the cessation of pain and rapid return to a normal blood amylase by 24 hours after operation. There have been no further attacks for 11 months following vagotomy.

CASE 11.—M. M., a 39-year-old veteran, was first admitted on Jan. 8, 1948, with a 5-year history of attacks of epigastric pain approximately once each month, on one occasion being associated with jaundice. The pain had become increasingly severe, and was accompanied by nausea and vomiting. The patient had been hospitalized on 3 occasions in 1946. In November, 1947, cholecystectomy was performed elsewhere. The gall bladder was described as containing stones. Approximately 4 weeks after operation excruciatingly severe abdominal pain developed, which the patient stated was the same pain he had had for the previous 5 years. In December, 1947, 600 c.c. of milky fluid were removed from a cystic abscess in the body of the pancreas. Profuse drainage from the cyst had continued until this admission. Physical examination revealed a sinus draining clear, mucoid fluid from the lateral aspect of

an oblique surgical incision. Constant suction was instituted in an effort to close the cyst. It continued to drain approximately 600 c.c. of pancreatic juice each 24 hours. On March 12, 1948, an exploratory laparotomy was carried out at which time a large, thin-walled pseudocyst of the lesser bursa was found. The cyst could not be enucleated or marsupialized, and after biopsy was done, drainage was re-established. The patient was discharged with the fistulous tract draining profusely.

The patient returned to the hospital on Nov. 19, 1948, because of cessation of drainage associated with abdominal pain. Blood amylase was 53.7 at this time, cyst amylase was 840. The sinus was opened and drainage resumed.

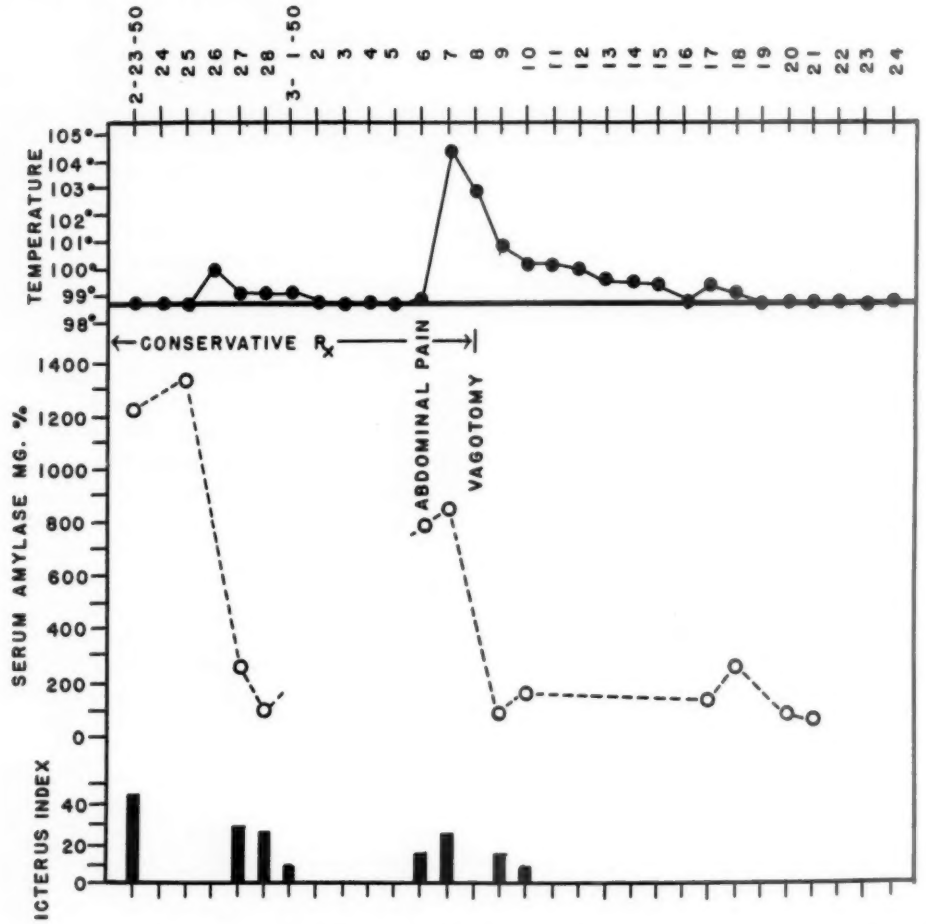


Fig. 1 (Case 7).—Note second acute attack while under conservative therapy. Vagotomy accompanied by rapid fall of amylase and icterus.

The patient again returned to the hospital in February of 1949, and a curettage of the cyst wall was done without decrease of the drainage. A therapeutic trial with tincture of belladonna was followed by virtual cessation of drainage. A vagotomy was recommended but the patient refused.

The patient was admitted again on July 28, 1950, having continued to drain a thick, clear fluid from the pancreatic fistula. The blood amylase was 110; amylase from the drainage was 1,578. The fistula fluid amylase did not rise appreciably with the injection of 1 mg. prostigmine. A Hollander test was performed and with hypoglycemia the fluid amylase rose from 4,160 to 7,700 (Fig. 2, *B*). On Aug. 8, 1950, the patient became enraged when the nurse refused him a narcotic for pain and the amylase value of the fistula secretion rose to

16,152 mg. per cent. Atropine (0.0004 mg.) was immediately administered and 30 minutes later the fistula amylase was 132 mg. per cent (Fig. 2, *A*).

On Aug. 11, 1950, a subdiaphragmatic vagotomy was carried out. The common duct was found to be thin-walled, and without stones. A probe was easily passed into the duodenum; cholangiograms showed no pancreatic reflux. The entire pancreas was thickened and nodular.

The opportunity to study extensively the influence of vagotomy on the fistula fluid was eagerly anticipated, but drainage ceased entirely in the first 24 hours postoperatively. The epigastric pain which the patient had experienced for 7 years has disappeared, and the 6-month postoperative checkup revealed the patient to be still free of pain and to have gained 30 pounds in weight. He has had no drainage from the healed fistulous tract.

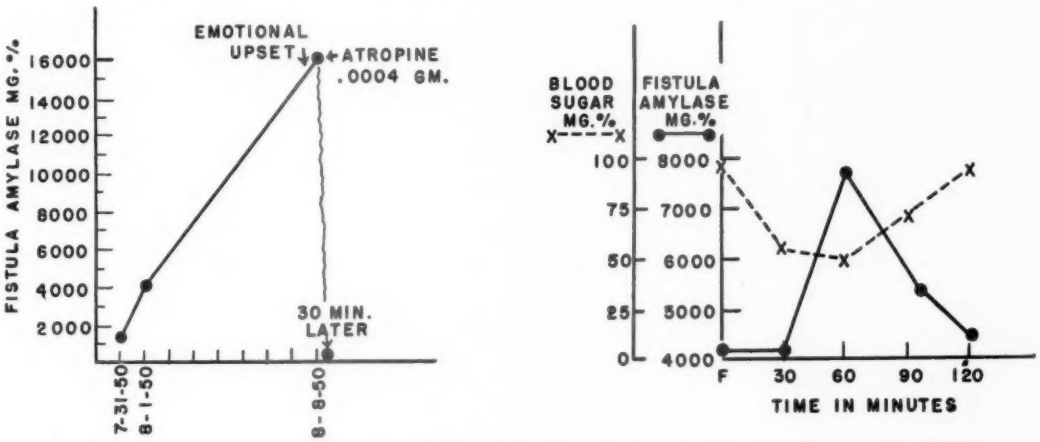


Fig. 2 (Case 11).—*A*, Effect of emotion on fistula amylase, abolished by atropine. *B*, Effect of hypoglycemia on fistula amylase.

This patient had a pancreatic fistula for 32 months. He demonstrated the relation of emotion to pancreatic secretion with a rise of fistula amylase to 16,152 mg. per cent in a brief period of rage. Injection of 0.0004 Gm. of atropine reduced the amylase to 132 mg. per cent 30 minutes later. Drainage ceased on the first day following vagotomy, has not recurred in 6 months, and the patient has had no further pain.

OPERATIVE FINDINGS (TABLE II)

Pancreas.—In all patients the gland was grossly abnormal to appearance and palpation. In most, the entire gland was changed, characterized by an increased firmness, irregularity, and loss of normal lobulation. In some, these changes were worse in the region of the head, while in 2 they were confined to the body and tail.

Gall Bladder.—Two patients had had a previous cholecystectomy. Of the remaining 9, 8 were normal and one had a gall bladder which contained stones. One of these normal gall bladders was removed, early in the series, on the basis of the older concepts. None of the other 7 gall bladders was excised.

Common Duct.—All 11 had a normal-appearing common duct. Ten were normal to exploration and/or cholangiogram. In 7 the duct was opened, explored, T tube inserted, and cholangiogram performed. In the remaining 3, cholangiograms were performed via a needle (2 cases) or the cystic duct (1 case). The T tubes were removed in 10 to 14 days, and bile drainage promptly ceased.

Cholangiograms.—These were performed on the operating table in 10 cases, by the methods previously described. Seven of the 10 failed to show reflux of dye into the pancreatic duct (Fig. 3, *A*).

TABLE II

CASE NO. AND AGE	MONTHS POST-OP.	FINDINGS AT OPERATION				GASTRO-ENTEROSTOMY	HOLLANDER TEST PRE-OP / POST-OP	WT. GAIN IN POUNDS	RETURN TO WORK	RECURRENT ATTACKS	RESULTS
		GALL BLADDER	COMMON DUCT	CHOLANGIO-GRAMS	PANCREAS						
1. M.C. 46	22	NORMAL THIN-WALLED	NORMAL	NOT DONE	FIBROTIC AND ATROPHIC	ADDED 1 YEAR AFTER VAGOTOMY	DIABETIC PHASE / 0°–0°	20	YES	NONE	IMPROVED (SEE CASE HISTORY)
2. L.H. 33	21	NORMAL THIN-WALLED CHOLECYS-TECTOMY	"	NO REFLUX	FIBROTIC IRREGULAR HARD	NONE	— / 18°–22°	30	"	"	MARKEDLY IMPROVED (SEE CASE HISTORY)
3. W.S. 36	20	NORMAL THIN-WALLED	"	"	ENLARGED, FIRM NODULAR	ADDED 1 YEAR AFTER VAGOTOMY	— / 0°–8°	15	"	"	MARKEDLY IMPROVED
4. E.H. 31	18	"	"	"	IRREGULAR FIRM ATROPHIC	NONE	20°–110° / 4°–10°	30	NO HAS PUL. TB.	"	MARKEDLY IMPROVED TREATED ELSEWHERE FOR TUBERCULOSIS SINCE THAT TIME
5. G.B. 34	13	"	"	"	IRREGULAR FIBROTIC ATROPHIC	NONE	2°–24° / 2°–3°	5	YES	2 EPISODES OF MILD ABDOM. PAIN ?PANCREATITIS	IMPROVED
6. R.H. 33	13	"	"	"	LARGE, IRREG. FIRM—ESPECIALLY IN REGION OF HEAD	ADDED 1 YEAR AFTER VAGOTOMY	0°–49° / 0°–4°	70	"	NONE	MARKEDLY IMPROVED
7. T.J. 38	11	PREVIOUSLY REMOVED	"	REFLUX	ENTIRE GLAND LARGE, THICK EDEMATOUS	NONE	— / 0°–0°	22	"	"	MARKEDLY IMPROVED (SEE CASE HISTORY)
8. R.S. 34	10	STONES CHOLECYS-TECTOMY	"	NO REFLUX	HEAD LARGE AND FIRM	NONE	0°–75° / 0°–0°	10	"	"	MARKEDLY IMPROVED
9. L.R. 49	8	NORMAL THIN-WALLED		REFLUX	LARGE TAIL FIRM THROUGHOUT	SIMULTANEOUS & VAGOTOMY ANTERIOR DUOD. ULCER	0°–44° / 0°–4°	2	"	"	"
10. M.D. 42	8	"	"	"	FIRM AND FIBROTIC IN HEAD + TAIL	NONE	0°–44° / 9°–28°	17	"	"	"
11. M.M. 39	8	PREVIOUSLY REMOVED	"	NO REFLUX	THICK IRREGULAR ESPECIALLY HEAD	NONE	0°–84° / 0°–0°	30	"	"	MARKEDLY IMPROVED (SEE CASE HISTORY)

RESULTS (TABLE II)

The patients were seen in the hospital at 3, 6, 9, 12, 18, and 22 months. All cases were followed and blood amylase, Hollander, and gastrointestinal barium studies were repeatedly performed.

Gastric Retention.—In only one patient (Case 9) was a simultaneous gastroenterostomy done. An anterior duodenal ulcer was also present, but it could have had no anatomic relationship to the cause of the pancreatitis.

Three had gastroenterostomy performed approximately 1 year after vagotomy. It would have been possible to have foreseen this, in these particular patients, because of the duodenal deformity present at the time of vagotomy. Moderate retention was present early and was intermittent for the first year. The usual symptoms of gas, fullness, eructation, and occasional diarrhea were present, although the patients had gained weight and were free of episodes of pancreatic type pain. These symptoms were much improved following gastroenterostomy.

The remaining 7 patients had mild to moderate early postoperative retention, similar to that encountered following vagotomy for duodenal ulcer, without preoperative obstruction. On the whole they seemed slower to recover adequate motility than ulcer patients. Several required small doses of urecholine, with meals, for the first 1 to 2 postoperative months. In no instance did urecholine administration give rise to pain. Gradually the retention decreased and apparently none of them will require a gastroenterostomy.

Recurrence of Pancreatitis.—Ten patients have had no recurrence of pancreatic pain. Several of them, in the first 2 to 3 months, were not entirely satisfied with their progress. However, the symptoms were always those of gastric retention and could be relieved by urecholine. On no occasion was there any elevation of temperature, pulse, or blood amylase and there was no tenderness over the pancreas. One patient (Case 5), early following vagotomy, returned twice requesting narcotics for pain. He had been a narcotic addict preoperatively and it has been quite difficult to get him to withdraw from drugs. On these outpatient visits none of these objective signs was present and we do not believe the patient had a recurrent attack. At one year following vagotomy he seems to be well and states he no longer takes narcotics.

Weight Gain.—In 8 cases, the gain has approached the weight lost during their disease. In 2 the gain is one-half of the weight loss. One patient (Case 1), who had pancreatic insufficiency, has recovered 20 of 40 pounds lost.

Ability to Work.—One patient developed pulmonary tuberculosis and is under hospital therapy for this disease. All others have been able to carry on gainful occupation without the necessity of hospitalization for recurrent attacks of pancreatitis.

Classification of Results.—All 11 patients are definitely improved. We believe 9 are markedly improved because of the results just listed. One patient (Case 1), listed as improved, had prevagotomy pancreatic insufficiency and still requires pancreatin for proper digestion and absorption of food. The symptoms of insufficiency definitely were not improved by vagotomy. However, his diabetes has gradually abated in severity and is now controllable by diet, whereas formerly he required 20 units of protamine zinc insulin daily. Because of the two questionable attacks in the patient with several narcotic addiction, he was also classed as only improved.

DISCUSSION

The definite improvement obtained by 11 consecutive patients as a result of vagotomy lends validity to the concept that recurrent acute pancreatitis may be of psychogenic origin. The pathogenetic sequence of pancreatic duct spasm accompanied by high enzyme secretion, secondary to vagus stimulation, has been shown experimentally to result in pancreatitis with necrosis.

It is undoubtedly true that, in a small percentage of the total cases, organic disease of the gall bladder and ductal systems will lead to this entity—for example, impacted ampullary stones, supraduodenal common duct stone, posterior duodenal ulcer, duodenal diverticulum, metaplasia of the pancreatic duct, and carcinoma of the pancreas. Autopsy evidence,[6, 7, 8] clinical reports of a low

incidence of associated cholelithiasis,[9, 10] and failure of recovery following cholecystectomy[11] indicate that the primary etiology does not lie in this area. Perhaps when they do occur together the association is more coincidental than causal. In our series, 2 patients had previous cholecystectomy without relief. Eight of the remaining 9 had a normal cholecystogram and no stones were present at exploration. Not one of the 11 had stones in the common duct.

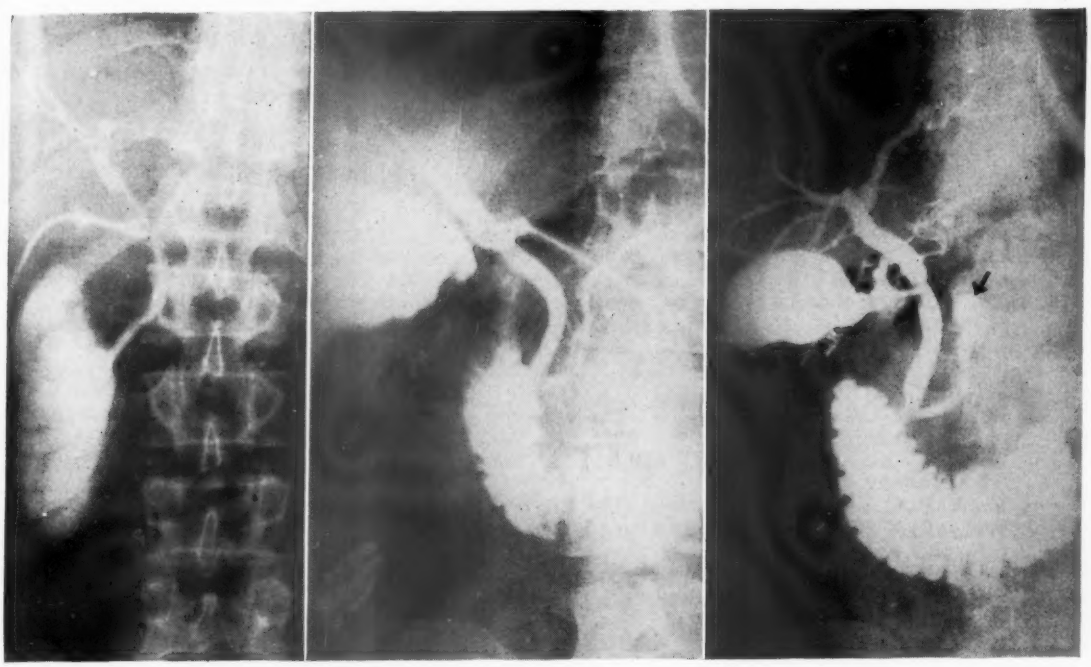
It seemed imperative to determine if organic ampullary obstruction or pancreatic reflux were present in our cases. Consequently, in 10 of the 11 this was determined by exploration of the common duct and/or cholangiogram. Seven had exploration and T tubes were inserted. The short period of such drainage was not sufficient to result in the long-term improvement observed. As a matter of fact, the 4 patients not having common duct drainage did equally as well as the others. In 7 cases, still having a normal gall bladder, cholecystectomy was not done. Their improvement therefore could not be ascribed to absence of the concentrated gall bladder bile, believed so important by advocates of this etiological concept.

Three newer forms of surgical therapy have been proposed for this serious disease—section of the sphincter of Oddi, partial gastric resection, and vagotomy.

Doubilet and Mulholland[1] believe spasm of the sphincter of Oddi leads to reflux of bile into the pancreatic duct and thus to pancreatitis. In our series only 3 of 10, having cholangiograms performed, had such reflux. If ampullary spasm produces pancreatitis from blockage of pancreatic secretion alone, and reflux of bile is not a major factor, sphincterotomy would still be as effective as it now is. Conversely, even if reflux of bile were produced by ampullary spasm, vagotomy could also be effective. If both it and sphincterotomy gave equal relief, which then would be preferable? Doubilet and Mulholland stated that many of these patients have other symptoms of parasympathetic overactivity that could not be affected by sphincterotomy.[36] The question still remains whether long-term scarring will result in stricture formation. Their follow-up studies indicate that this, and the possibility of ascending infection, seem to be of little clinical significance. However, the experimental work of Mallet-Guy and associates[37] showed that with sphincterotomy, all 8 experimental animals developed infection of the gall bladder and common duct walls. Gray and associates[38] noted similar changes in 7 of 10 dogs and 3 of the 10 also developed severe hepatitis. In some patients, with previous attacks, stricture or occlusion may develop in the pancreatic duct system far removed from the ampullary region. In Case 9 (Fig. 3, *C*) the head of the pancreas appeared little changed, but there were marked changes in the body and tail. It is difficult to see how sphincterotomy would have helped this patient. We believe also that, from the technical standpoint, vagotomy is an easier operative procedure.

Richman and Colp[32, 33] seem to feel that the partial gastrectomy, rather than vagotomy, was the major factor in the improvement of 2 of 3 cases they reported. The decreased secretin formation perhaps resulting from diversion of the gastric contents to the upper jejunum was assumed to be the mechanism producing the relief. Also mentioned was the prevention of ampullary spasm by this procedure. However, that the type of pancreatic secretion, resulting

from secretin, does not have the same malign potentiality as that from vagal excitation is suggested also by the experimental work of Popper and co-workers.[30] These investigators were unable to cause pancreatitis and necrosis with repeated injections of secretin, even though the pancreatic ducts were ligated. Gastric resection is a more formidable procedure than vagotomy.



A. *B.* *C.*

Fig. 3.—*A* (Case 2), Note absence of pancreatic reflux. *B* (Case 10), Note reflux into normal pancreatic duct. *C* (Case 9), Note reflux into abnormal duct. Obstruction indicated by arrow.

The two patients of Rack and Elkins[34] failed to obtain benefit from vagotomy. The explanation of our different results may reside solely in the statistical realm of the expected percentage of relief of recurrent pancreatitis by vagotomy. Since no Hollander tests were reported by them, there is no assurance that complete vagotomies were accomplished. As mentioned previously, the posterior nerve may be easily overlooked, especially if past inflammatory changes in this area have obscured the normal anatomy. We have observed also that the full benefits of vagotomy have often not been apparent until normal gastric motility reappears. This may be delayed for 1 to 2 months postoperatively.

Vagotomy can produce several results which should influence favorably the course of recurrent acute pancreatitis, as follows: (1) prevent any ampullary and pancreatic duct spasm of psychogenic origin[27, 29]; (2) prevent increased pancreatic enzyme production of psychogenic origin[2, 5, 17-19, 22, 24, 28]; (3) decrease the enzyme secretion resulting fom the presence of peptones and hydrochloric acid in the duodenum[22]; (4) prevent increased hydrochloric acid production by the stomach in response to emotional stimuli—this would secondarily reduce sphincter spasm and pancreatic enzyme production resulting from such in-

creased acidity; (5) ameliorate the effects of the increased gastric acidity formed in response to excessive alcohol intake. We believe that the explanation of the definite improvement derived by our patients lies in various combinations of the preceding potential beneficial effects of vagotomy.

CONCLUSIONS

1. On the basis of a theory that psychogenic stimuli have an important role in the etiology of recurrent acute pancreatitis, treatment by vagotomy is proposed.

2. Vagotomy performed upon 11 patients, chosen because of the marked progression of their disease, resulted in definite improvement in all.

REFERENCES

1. Doubilet, H., and Mulholland, J. H.: Recurrent Acute Pancreatitis: Observations on Etiology and Surgical Treatment, Ann. Surg. **128**: 609, 1948.
2. Schaffarzick, W. R., Ferran, H., and McCleery, R. S.: A Study of the Effect of Vagotomy on Experimental Pancreatitis, Surg., Gynec. & Obst. To be published.
3. Opie, E. L.: The Etiology of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **12**: 182, 1901.
4. Ravdin, I., and Johnston, C. G.: The Etiology and Pathogenesis of Acute Hemorrhagic Pancreatitis, Am. J. M. Sc. **205**: 277, 1943.
5. Lium, R., and Maddock, S.: Etiology of Acute Pancreatitis; an Experimental Study, SURGERY **24**: 593, 1948.
6. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, Arch. Surg. 6: 1, 1923.
7. Rienhoff, W. F., and Pickrell, K. L.: Pancreatitis. An Anatomic Study of the Pancreatic and Extra-Hepatic Biliary Systems, Arch. Surg. **51**: 205, 1945.
8. Edmondson, H. A., Bullock, W. K., and Mehl, J. W.: Chronic Pancreatitis and Lithiasis. I. A Clinicopathologic Study of 62 Cases of Chronic Pancreatitis, Am. J. Path. **25**: 1227, 1949.
9. Gambill, E. E., Comfort, M. W., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: An Analysis of 27 Cases Associated With Disease of the Biliary Tract, Gastroenterology **11**: 1-33, 1948.
10. Muether, R. O., and Knight, W. A., Jr.: Chronic Recurrent Pancreatitis. I. Clinical and Laboratory Aspects, Gastroenterology **12**: 24, 1949.
11. Northman, M. M.: Chronic Relapsing Pancreatitis, Bull. New England M. Center **11**: 182, 1949.
12. Archibald, E.: Lewis Practice of Surgery, Vol. 7, Hagerstown, Md., 1933, W. F. Prior Company, Inc., p. 1.
13. Lewis, F. J., and Wangensteen, O. H.: Antibiotics in the Treatment of Experimental Acute Hemorrhagic Pancreatitis in Dogs, Proc. Soc. Exper. Biol. & Med. **74**: 453, 1950.
14. Babkin, B. P.: Secretory Mechanism of the Digestive Glands, New York, 1944, Paul B. Hoeber, Inc.
15. Rich, A. R., and Duff, G. L.: Pathogenesis of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **58**: 215, 1936.
16. Wangensteen, O. H., Leven, N. L., and Manson, M. N.: Acute Pancreatitis (Pancreatic Necrosis): Experimental and Clinical Study, With Special Reference to Significance of Biliary Tract Factor, Arch. Surg. **23**: 47, 1931.
17. Mellanby, J.: Quoted from Best and Taylor: Physiological Basis of Medical Practice, ed. 4, Baltimore, 1945, Williams & Wilkins Company.
18. Routley, E. F., Mann, F. C., Bollman, J. L., Grindley, J. H., and Flock, E. V.: Effects of Vagotomy on Pancreatic Secretion, Proc. Staff Meet. Mayo Clin. **25**: 218, 1950.
19. Kuntz, A., and Richins, C. A.: Effects of Direct and Reflex Nerve Stimulation on the Exocrine Secretory Activity of Pancreas, J. Neurophysiol. **12**: 29, 1949.
20. Selye, H.: Textbook of Endocrinology, Montreal, 1947, Acta Endocrinol. Univ. de Montreal, p. 850.
21. Bayliss, W. M., and Starling, E. H.: Quoted from Best and Taylor, Physiological Basis of Medical Practice, ed. 4, Baltimore, 1945, Williams & Wilkins Company.
22. Thomas, J. E., and Crider, J. O.: The Pancreatic Secretagogue Action of Products of Protein Digestion, Am. J. Physiol. **134**: 656, 1941.
23. Bockus, H. L.: Gastroenterology, Philadelphia, 1946, Vol. 3, W. B. Saunders Company.
24. Wener, J., Simon, M. A., and Hoff, H. E.: Production of Acute Pancreatitis in Dogs by the Administration of Mecholyl, Gastroenterology **15**: 125, 1950.

25. McGowan, J. J., Butsch, W., and Walter, W.: Pressure in the Common Bile Duct of Man. Its Relation to Pain Following Cholecystectomy, J. A. M. A. **106**: 2227, 1936.
26. Elman, R.: Surgical Aspects of Acute Pancreatitis with Special Reference to its Frequency as Revealed by the Serum Amylase Test, J. A. M. A. **118**: 1265, 1942.
27. Von Anrep, G.: The Influence of the Vagus on Pancreatic Secretion, J. Physiol. **50**: 421, 1915-16.
28. Pavlov, I. P.: Quoted from Best and Taylor: Physiological Basis of Medical Practice, ed. 4, Baltimore, 1945, Williams & Wilkins Company.
29. Doubilet, H., and Mulholland, J. H.: The Surgical Treatment of Recurrent Acute Pancreatitis by Endocholedochal Sphincterotomy, Surg., Gynec. & Obst. **86**: 295, 1948.
30. Popper, H. L., Necheles, H., and Russell, K. C.: Transition of Pancreatic Edema Into Pancreatic Necrosis, Surg., Gynec. & Obst. **87**: 79, 1948.
31. Rienhoff, W. F., and Baker, B. M.: Pancreolithiasis and Chronic Pancreatitis, J. A. M. A. **134**: 20, 1947.
32. Richman, A., and Colp, R.: Chronic Relapsing Pancreatitis Treatment by Subtotal Gastrectomy and Vagotomy, Ann. Surg. **131**: 145, 1950.
33. Richman, A., Colp, R., and Lester, L. J.: Subtotal Gastrectomy for Pancreatitis, Gastroenterology **16**: 267, 1950.
34. Rack, F. J., and Elkins, C. W.: Experiences With Vagotomy and Sympathectomy in the Treatment of Chronic Recurrent Pancreatitis, Arch. Surg. **61**: 937, 1950.
35. McCleery, R. S., Kesterson, J. E., and Proffitt, J. N.: Technique for, and Results of, a Dependent, Greater Curvature Gastro-Enterostomy, Ann. Surg. To be published.
36. Doubilet, H., and Mulholland, J. H.: Surgical Treatment of Calcifications of the Pancreas, Ann. Surg. **132**: 786, 1950.
37. Mallet-Guy, P., Auger, L., and Billa, M.: Quoted by Gray, S. H., and others: Chronic Cholecystitis Produced by Division of the Sphincter of Oddi, Arch. Surg. **59**: 1007, 1949.
38. Gray, S. H., Probstein, J. G., and Sachar, L. A.: Chronic Cholecystitis Produced by Division of the Sphincter of Oddi, Arch. Surg. **59**: 1007, 1949.

DISCUSSION ON "SURGICAL THERAPY FOR CHRONIC PANCREATITIS" BY DR. RALPH F. BOWERS, AND "A CLINICAL STUDY OF THE EFFECT OF VAGOTOMY ON ACUTE RECURRENT PANCREATITIS" BY DR. ROBERT S. McCLEERY, DR. JOHN E. KESTERSON, AND DR. WILLIAM R. SCHAFFARZICK

DR. EDGAR J. POTH.—I should like to support Dr. Bowers' observations with some we have made. I have used the Roux Y technique to drain the biliary tract for recurring chronic pancreatitis in five instances. The first case was done about 2½ years ago. The common duct was divided and transplanted into the side of the jejunum of a Roux Y loop. I believe it best to anastomose the split end of the common duct to the side of the jejunum rather than into the end of the Roux-Y limb, because a more accurate mucosa-to-mucosa suture can be performed with less likelihood of subsequent structure formation at the site of anastomosis. The remaining four patients still had their gall bladders, which were relatively normal and contained clear bile. These patients were subjected to Roux-Y cholecystjejunostomy. The common duct was not divided. Thus the biliary tract was decompressed through the gall bladder into a defunctionalized loop of jejunum. All of these patients have done well.

I have certain misgivings regarding the blind division of the sphincter of Oddi. Subsequent scar formation might well be a worse situation than was initially present. When the sphincter is adequately opened under direct vision and the mucosal edges are approximated, the biliary tract is exposed to the danger of regurgitation of food from the duodenum.

We did cholecystjejunostomosis using the Roux Y technique with the jejunal limb at least 15 inches long on dogs. We then did bacteriologic studies on the contents of the gall bladder and jejunal loop at varying levels. Although no food regurgitated into the gall bladder and the bile was entirely clear, large numbers of bacteria were always found in the gall bladder. There was no evidence of cholangitis. However, had the bowel loop not been defunctionalized and food been forced into the gall bladder or biliary tract, a real hazard of infection might well exist.

DR. HARRIS B. SHUMACKER, JR.—I certainly enjoyed these two very stimulating papers. They represent a physiologic approach to treatment of chronic recurrent pancreatitis.

Dr. Moore and I have been interested in this problem for only a short while. However, during the past seven months we have treated nine patients by transduodenal section of the sphincter with actual excision of a portion of the sphincter for microscopic study. Our patients have been a good bit older than those of Dr. Bowers. Seven of the nine were over 50, four over 60, and two over 70 years of age.

In spite of the short period of our study we have been impressed with certain observations: First, the amylase curve after Prostigmine stimulation is a very helpful diagnostic tool in this particular condition. In the second place, the sphincter seems pretty regularly to be abnormally tight, although we have not seen microscopic evidence of any demonstrable organic change. In the third place, we are quite convinced from our short experience that common duct drainage should be carried out when the sphincter is divided. In four of these nine cases there was a very transient postoperative rise in blood amylase and interestingly enough in two of the four we did not drain the common duct while in the other two the rise in amylase occurred when the tube was clamped prior to its withdrawal. One of these patients developed, I believe as a result of transient edema as evidenced by the rise in blood amylase, a pancreatic abscess which had to be drained. The rest of the patients have done quite well. I believe it would be quite helpful to use a vagal blocking agent during the immediate postoperative course. We intend to do so in the future.

Dr. Doubilet showed in dogs that if one cuts the sphincter the gall bladder becomes functionless. In all except one of our patients the gall bladder was diseased and was excised or had been previously removed. Interestingly enough, in the exceptional patient cholecystograms made some months after operation were quite normal. None of the patients has had pain since operation. One of the patients was a confirmed morphine addict and his total drug intake since operation about 7 months ago was one 75 mg. dose of Demerol. During the recent cold wave in the Middle West one of these patients drove all the way from Iowa over icy roads so that we could obtain cholecystograms because he was so grateful for the remarkable relief of the pain that he has had. Whether future trouble will ever develop because of reunion and stenosis of the divided sphincter remains to be seen and only years will tell. Actually it is well known that when other sphincters are cut by accident or on purpose they have not tended to regain function. I should expect the same to be true of the sphincter of Oddi.

DR. FREDERICK M. OWENS, JR.—I would like to add a couple of supporting remarks to what Dr. Hay has said. We have been very much pleased with this procedure of transplantation. In studies of these patients before operation we have determined the sphincter dynamics by the use of Banthine. We have found that the Banthine has had no effect whatsoever on the sphincter. All of these patients have had elevated sphincter resistance. In discussing the problem with Dr. Dragstedt, he said that he has been dissatisfied with the results of vagotomy in these patients with pancreatitis. I think that there are several mechanisms for pancreatitis, the most prominent being the common channel. Certainly this procedure offers considerable aid in those patients who have a pancreas which can be handled well. In those not handled well, I think that the Roux Y is applicable.

DR. CLARENCE DENNIS.—I would like to point out one procedure which had been suggested long before I undertook it, only to emphasize that it is not the proper thing to do: that is total resection of the pancreas in these patients who have had a great deal of trouble. We had a 58-year-old woman who came to the Minneapolis General Hospital, who had had an elevated serum amylase level over a period of weeks. She had become addicted to opiates, and the Medical Service despaired her survival. She had had subphrenic abscesses and explorations in order to establish the diagnosis. She had had her gall bladder out and so on. We undertook to take out the pancreas and something over a year ago spent from the early morning until late in the evening working on this particular individual. It was a very trying, and at times a hair-raising, experience throughout the day. During the operative procedure it was also impossible to identify the celiac axis for one thing. We had to borrow tissue from other places to close defects in the portal vein for another thing. It is a procedure which should be avoided if it is possible to do so. She recently returned to celebrate

her first anniversary by getting along on 20 units of insulin a day, carrying out her duties as a housewife, having no further pain, and apparently maintaining her weight at a little above what it was at the time of her surgery. The end result is satisfying, but it is a tightrope act to get here.

DR. KEITH S. GRIMSON.—I would like to add one comment. Perhaps in patients with early stages of this complicated problem of pancreatitis use of parasympathetic drugs as continuous treatment would be worth while. It has been Dr. Shingleton's experience that symptoms are often relieved. Perhaps in later stages or with more complicated problems when one does explore the abdomen one of the several operative procedures discussed might be used. However, if the pancreas is large and inflammatory involvement extensive one might better consider relief of pain by a celiac ganglionectomy. This operation may be tedious, but it can be done through any upper abdominal approach and the results observed thus far over a period of six years have been good. One word of caution which I know the speakers recognize should be added. This is that the period of observation of many of the patients presented this morning has been less than one year. Chronic pancreatitis runs a fluctuation course. Late results of these several studies will be very interesting.

DR. RALPH F. BOWERS (Closing).—I have tried to establish experimentally the role of sphincter spasm in this disease, but have not been able to do it. The value of the nerve cutting operations would be clarifed if relief of spasm could be accomplished by these operations. It is to be hoped that a method for actual measurement of the spasm will be devised. Another thought about relieving regurgitation of bile might entail retrograde pancreaticojejunostomy—that is, by amputating the tail of the pancreas and anastomosing the pancreatic duct to the jejunum en Roux Y. This would be a simpler procedure.

I agree with Dr. Grimson about the short follow-up period. One case has gone over two years but that is probably not long enough to be certain of the permanency of relief of symptoms. At any rate, I am pleased that surgeons are interested in this disease and gratified to see encouraging results.

Dr. McCleery's idea is interesting and worth while. His results so far are good. I congratulate him and hope he will keep us informed of his patients' progress. Vagotomy, however, may prove to afford temporary relief because many reports indicate that the completeness of the nerve interruption may not persist. What was thought to be complete interruption two years age is not now complete. Certainly vagotomy is simpler than choledochojejunostomy, and I hope Dr. McCleery's method proves to be the correct one and that the relief will be permanent.

DR. ROBERT S. McCLEERY (Closing).—I wouldn't want this to wind up as a Mutual Admiration Society between Dr. Bowers and me. I would like to agree with him, and also Dr. Poth, and in part with Dr. Shumacker. Their work with diversion of the bile means a great deal, I am sure, if they can relieve all of the symptoms by such diversion. Then spasm, in which we believe, most probably would be deleterious by causing reflux. I do not mean to imply, however, that the idea of cholecystitis, cholelithiasis, and common duct stone is necessarily involved, and I don't think that they would say that either. I differ with Dr. Shumacker on the Prostigmine amylase test. We have done it on all of our patients and the results have been highly unsatisfactory, in a diagnostic sense. Common duct drainage following sphincterotomy, where there will be postoperative edema, seems indicated, but I do not believe it necessary where vagotomy is done in the presence of a normal common duct. Dr. Hay I can agree with because I think if his operation works, which I am sure it does, it could work on the same basic etiological principle that we believe to be the true one. To Dr. Grimson I would like to point out that in our series, 7 of the 11 have been followed between 1 and 2 years.

PREVENTION OF DILATATION IN AUTOGENOUS VENOUS AND PERICARDIAL GRAFTS IN THE THORACIC AORTA

An Experimental Study

Yoshio Sako, M.D.,* Minneapolis, Minn.

SINCE earlier systematic investigations into the use of blood vessel grafts by Carrel and Guthrie[1] in 1906, various investigators have favored the idea that autogenous grafts were preferable to homologous and heterologous tissues. This viewpoint was studied in some detail by Klotz, Permar, and Guthrie,[2] who felt that the use of autogenous grafts uniformly gave excellent results. Gross,[3] Shumacker,[4] Swan,[5] and associates have described excellent functional results after transplanting living or dead homologous or heterologous tissues. Since the sources of autogenous arterial grafts are obviously limited, an inventory was made of the body's own tissues which could be substituted as donor vascular segments. To this purpose the possibilities of utilizing pericardial grafts for bridging experimental defects in the thoracic aorta have been explored and reported elsewhere.[6] In the course of preliminary skirmishes with this problem the following complications have been met: (1) aneurysmal dilatation, (2) perforation and hemorrhage, (3) deposition of cholesterol on the grafts, and (4) unique features of endothelization of the grafts. With the hope of minimizing several of these difficulties, additional experiments have been carried through grafting venous segments into the aforementioned aortic segment of the dog. When a piece of unsupported vein several centimeters long is so placed, our experience confirms Carrel's observation[7] that similar grafts spliced into carotid artery defects rather uniformly dilated after about two weeks. Johnson and co-workers[8] too noted that long venous grafts in the abdominal aorta rather consistently underwent a fusiform dilatation. Also, hydraulically considered, the thoracic aorta pressures would seem to subject a graft to the maximal spreading force. All our grafts have been placed, therefore, just distal to the obliterated ductus arteriosus.

Since our preliminary results after transplanting either a pericardial tube or a venous graft into the thoracic aorta led invariably to a subsequent dilatation in that area, any method capable of avoiding this complication had probably best be thoroughly tested.

METHOD

Mongrel dogs weighing 8 to 20 kg. were used. The preoperative care, operative setup, anesthesia, and postoperative care of these have been outlined by us in previous communications.[9] The chest was entered through the left fifth intercostal space and the pericardium excised in a square sheet aver-

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*Fellow of the American Cancer Society.

aging 4 to 5 cm. on a side. The diameter of the aorta was measured with calipers and a suitable rigid mold, a small test tube or catgut tube of similar size, selected. The sheet of pericardium after removing the outside fat was then placed over the tube, cardiac side inward, and the longitudinal defect was sutured with 000000 mattress type of silk stitches 1 mm. apart. Any excess pericardium was trimmed down to within 2 mm. of the longitudinal suture line and this cuff reinforced with a running whipping stitch of 000000 silk just outside the mattress suture.

The thoracic aorta distal to the ductus arteriosus was freed, cross-clamped, and transected. In some instances the graft was inserted at this point; in most instances, however, the first two pair of intercostal arteries were doubly ligated and 2 to 3 cm. of aorta were excised. The grafts were then sutured into place with a running 000000 silk everting mattress suture. The aortic clamps were then released, the graft pleuralized, 100,000 units of penicillin left in the pleural space, the lungs re-expanded, and the chest wall closed in layers with silk. In later experiments, to prevent the dilatation soon detectable under the preceding technique, fascia lata was removed from the left thigh as a preliminary step to the thoracic procedure; then having prepared the pericardial graft as already described, the fascia lata was placed around the pericardial graft as an outer jacket. The ends of the pericardial and fascial tubes were sewn together with interrupted stitches to prevent slipping. Thus the combined graft includes both the layer of the pericardium and the layer of fascia.

Autogenous vein grafts were secured from the inferior vena cava above the common iliacs and below the renal veins. In dogs weighing up to 15 kg. the vena cava segment is approximately the same diameter of the thoracic aorta and in those weighing less than 8 kg. the segment is narrower than the thoracic aorta. Reinforcement of the vein grafts was carried out with fascia lata grafts in approximately the same manner as described for the pericardial grafts, save for the modification of delaying the complete suturing of the longitudinal defect of the fascia until the blood was already flowing through the graft. This permitted a more accurate tailoring of the graft to the size of the distended aorta. Dermis grafts and split-thickness skin grafts were similarly tested as a possible source of buttressing material. The latter were obtained from the dog's chest with the Padgett-Hood dermatome. Attempts to disinfect the skin were made by preoperative skin preparation with pHisoderm and G-11 packs to the donor skin, four to five days preoperatively. Too regularly, however, it appeared that pathogenic organisms re-

TABLE I. TYPE OF GRAFTS BRIDGING AORTIC DEFECTS

TYPE OF GRAFTS	NUMBER OF DOGS	NUMBER OF DOGS SURVIVING FOR STUDY	AGE OF OLDEST GRAFT IN SERIES
Pericardium	40	24	18 mo.
Pericardium and fascia	25	16	18 mo.
Vein	6	6	1 yr.
Vein and fascia	10	9	1 yr.
Vein and split-thickness skin or cutis	10	4	4 mo.

mained undestroyed deep within the interstices of these layers and, so protected, would ultimately flourish and destroy the graft's integrity. No total heparinization was employed in any animal but in some instances the grafts were dipped in heparin solution while the aorta was being prepared for inserting the graft.

Periodic aortograms were taken. These were made under general anesthesia by placing a catheter into the left common carotid artery and down near the aortic valves. Fifteen cubic centimeters of 35 per cent Diodrast were rapidly injected and the films were immediately exposed. After the catheter was withdrawn the defect in the artery was closed with 000000 arterial silk.

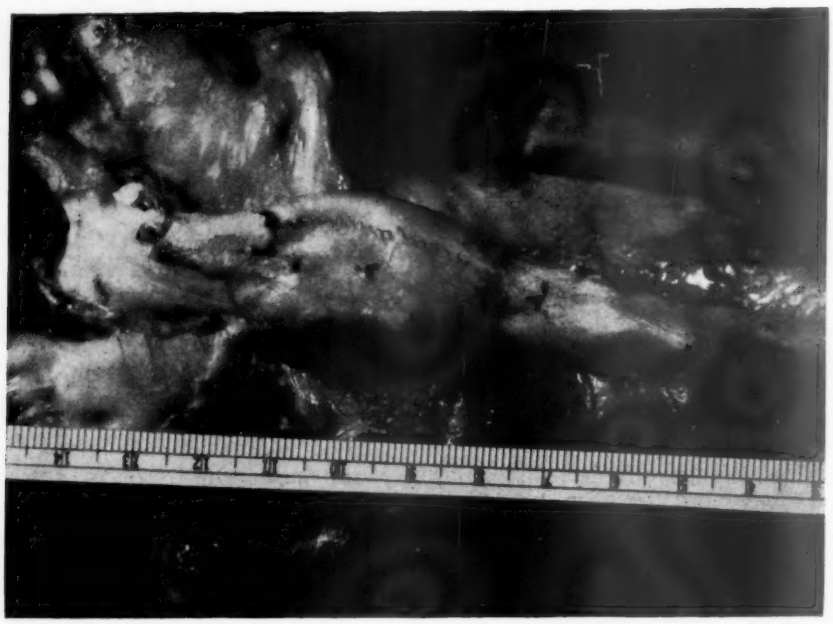

Fig. 1.—Pericardial graft, three months postoperatively. There is dilatation of the graft.

RESULTS

Table I shows the number and types of grafts which were constructed and the age of the oldest graft at the time of this report.

Forty pericardial grafts were constructed. Results of these experiments will be published in detail elsewhere.[6] Twenty-four dogs survived and were examined from periods of one month to eighteen months by roentgen studies, exploratory operation, and by necropsy. Three of these animals are being kept for long-term observations. At gross examination the grafted segments characteristically exhibited a dilatation in three to six weeks if the insert was longer than 2 cm. (Figs. 1, 2, and 3). On examination the internal aspects of the graft demonstrated a variety of appearances contingent essentially on the length of the postoperative period. It was apparent to us that several hours after the graft had been in place, a thin layer of fibrin and blood cellular elements deposited over the entire inner surface of the graft. Very rapidly an endothelial tissue encroachment from the adjacent aorta appeared and

this became quite apparent by the end of the first week. This creeping of the endothelium into both ends of the graft from the anastomotic line appeared to be accelerated by the presence of silk sutures used to close the longitudinal defect when the graft was constructed (Fig. 4). Placement of additional silk sutures longitudinally into the graft substantiated this observation. Apparently the silk sutures exposed to the lumen of the graft serve as a trellis for the invading endothelium. In grafts which dilated, there was not only

Fig. 2.—Aortogram, one month postoperatively, showing a 4 cm. pericardial graft with no dilatation. Distal point of anastomosis is hardly visible because of the accurate matching of the graft.

greater likelihood of thrombus formation, but an irregularity in the pattern of endothelization. In segments forty-five to ninety days old, a yellowish deposit in the central portions of the grafts was noted. Upon chemical analyses[10] this was found to be cholesterol ester which was present in concentrations up to four times as high as in the adjacent aorta.

Pericardial grafts buttressed with fascia were inserted into aortic defects in twenty-five dogs. There were eight deaths due to technical errors such as anesthetic difficulties or persistent pneumothorax. Two dogs died of distemper postoperatively. There were three deaths due to hemorrhage, one on the fifth postoperative day, one on the thirtieth postoperative day, and one

on the thirty-ninth postoperative day. In these animals it was noted that there was evidence of infection in the pleural cavity. With the use of antibiotics and stricter attention to aseptic technique, particularly the skin preparation, we were able to avoid this difficulty in all future operations in this group. Sixteen surviving dogs have been observed up to eighteen months.

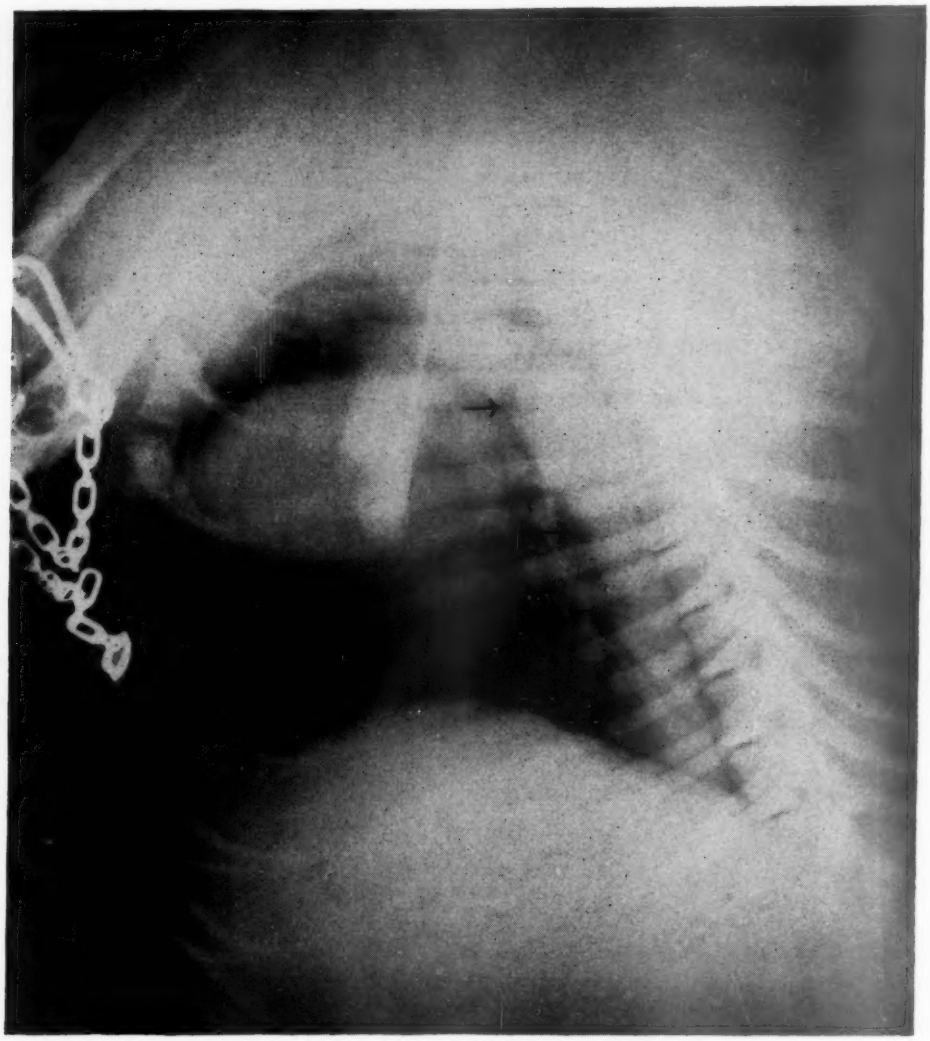

Fig. 3.—Aortogram of the same dog as shown in Fig. 2, one hundred sixty-eighth postoperative day. There is fusiform dilatation of the graft.

In this entire series periodic serial aortograms have shown no dilatation in any grafts supported by fascial tissue (Fig. 5). Gross examination of these grafts shows that endothelization crept forward in a more uniform manner and the soft yellow plaques noted in dilated pericardial grafts were no longer found (Figs. 6 and 7). Microscopic sections demonstrate endothelization of the older pericardial tubes and intact fascial support with proliferation of adventitial tissue around the graft.

Six dogs have been operated upon placing inferior vena cava autografts up to 4½ cm. in length into the aortic defects. Periodic serial aortograms have uniformly shown a fusiform dilatation of the venous grafts after about

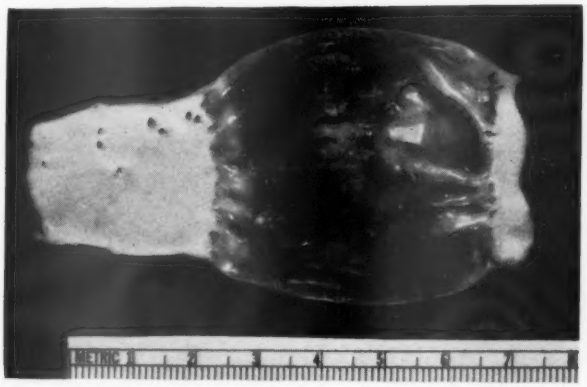

Fig. 4.—Pericardial graft 4½ cm. long, two months postoperatively. Endothelization progressing into the graft is greater along the longitudinal suture which is barely visible in the mid-portion of graft.

Fig. 5.—Pericardial graft supported by fascia lata, eight months postoperatively. There is no dilatation.

two to three weeks postoperatively (Figs. 8, 9, and 10). Serial aortograms suggest that very little further dilatation occurs after five to six months. No instance of cholesterol deposit in the dilated segment has been visible. It also appears that the vein need not undergo complete re-endothelization, since certain islands may survive and retain an identity. Although in some instances patches of the intima break down, these appear to re-endothelize rapidly.

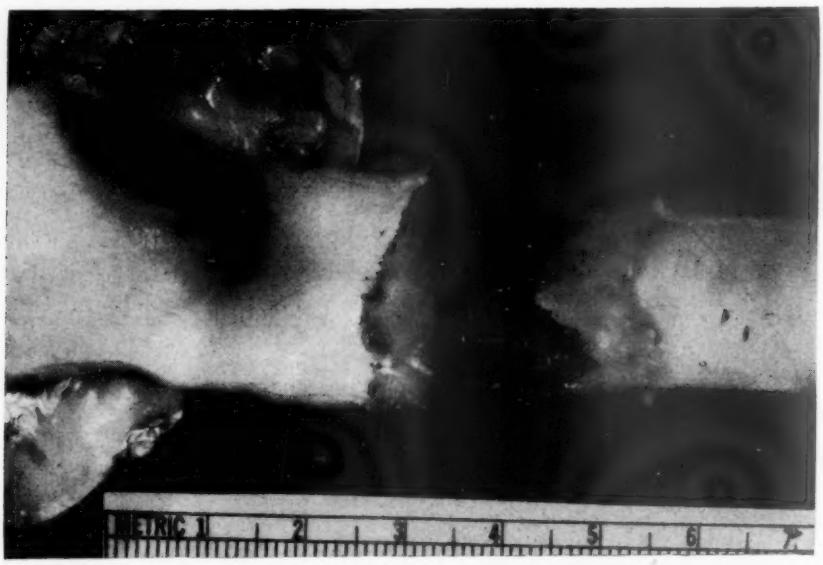

Fig. 6.—Pericardial graft supported by fascia, two months postoperatively. There is no dilatation. Progression of endothelization is well illustrated.

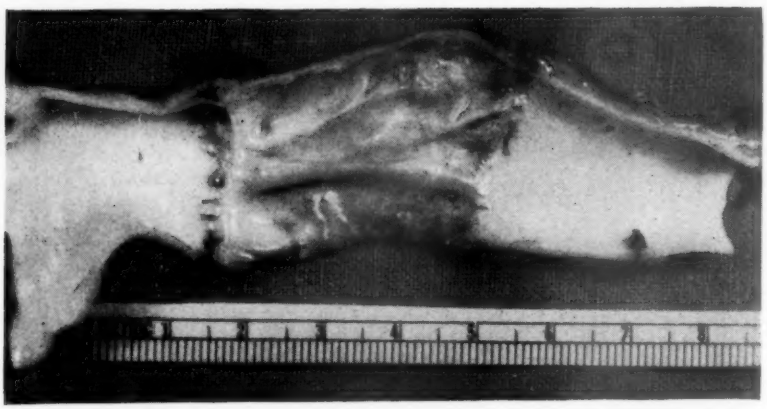

Fig. 7.—Pericardial graft supported by fascia, eight months postoperatively. There has been complete endothelization of the graft. (The ridges visible disappear when the graft assumes the tubular form.)

Ten dogs have been operated upon with grafting of fascially supported vena cava segments up to 4½ cm. long. There was one death due to distemper. At three weeks that graft showed no dilatation. The remaining nine dogs have had periodic serial aortograms from six months to fourteen months and these grafts have also apparently remained protected against dilatation

(Fig. 11). Gross examination shows fusion of vein and fascia as well as thickening of the vein (Fig. 12). The lining was very smooth. Results in this series were quite satisfactory. Microscopic sections show apparent survival of fascial tissue and survival and thickening of venous tissue with rapid and complete endothelization either by persistence of original endothelium or by new growth. In ten dogs vein grafts supported by either split-thickness skin or dermis were inserted into the thoracic aorta. The first six dogs died within

Fig. 8.—Autogenous venous graft, fourteen days postoperatively. The graft is identical in size with the adjacent aorta.

one month. In each instance there was evidence of severe infection around the graft and death was due to hemorrhage either from the suture line or from a ligated branch of the grafted vein. Four of the animals that died had a split-thickness skin graft supporting the vein, and two had dermal grafts. The problem appeared to stem from the fact that it is very difficult to rid the skin of bacteria which were present in the crypts around the hair shafts and follicles. In the last four dogs penicillin, 300,000 units daily for three weeks, was given. Of these four, one dog died. A clot had dissected into the space between the skin and vein. There was also evidence of infection around the

skin graft. The remaining three dogs have now been well up to three months. Two aortograms have been taken in each animal and in two there is no dilatation (Fig. 13). In one there was dilatation of the proximal anastomotic line. Microscopic sections from succumbing animals show evidence of survival of tissue around the graft.

Fig. 9.—Aortogram of the same dog shown in Fig. 8, three months postoperatively. A fusiform dilatation of the graft is now apparent.

DISCUSSION

With respect to survival of autogenous tissue grafts our findings are in agreement with those of Carrel and Guthrie,[1] Klotz, Permar, and Guthrie,[2] and more recently with the work of Shumacker and associates.[4] The pericardium may either serve as a scaffolding or as a framework for host tissues. A description of the entire role played is hardly possible from the evidence to date. Long-term survival studies should help clarify this point. The pericardial graft shows thickening with the ingrowth of endothelium in the lumen and with the proliferation of connective tissue from the outside. In some instanes there is evidence of fragmentation and hyalinization of pericardial

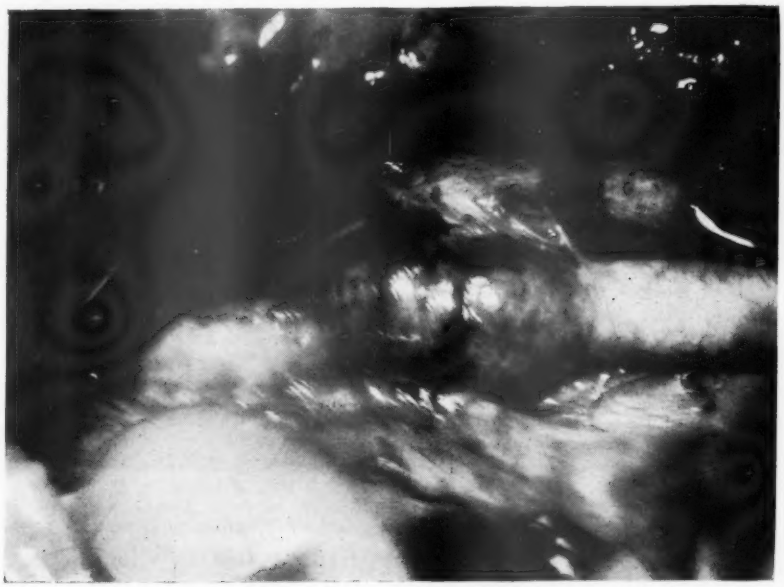

Fig. 10.—Photograph at exploratory operation of dog whose aortograms are shown in Figs. 8 and 9. The dilatation is quite apparent.

Fig. 11.—Vein graft supported by fascia, one year postoperatively. There is no dilatation of the graft. Graft is 3.8 cm. long.

Fig. 12.—Vein graft supported by fascia, fourteen months postoperatively. There is no dilatation. The entire graft lumen was smooth and glistening. (Buckled areas disappear when graft resumes the tubular form.)

Fig. 13.—Aortogram, three months postoperatively, showing support of vein graft with dermis.

tissue, but for the most part there are minimal degenerative changes. Autogenous fascial tissue has been employed for years as suture or for covering defects. Peer and Paddock[11] studied the histologic fate of deeply implanted autogenous dermal grafts and observed that skin of the abdomen with the epidermis removed and inserted beneath the skin of the chest remained in place and fused with the surrounding tissue. Use of dermis graft in repairing hernias is commonly employed and there is abundant evidence that such grafts survive.[12]

Autogenous vein grafts have been shown to have high incidence of survival.[2, 4] Detailed histologic studies of autogenous vein grafts have been reported by Shumacker and colleagues.[4] Our studies also show evidences of survival of smooth muscle, the presence of intact endothelium and elastic tissues, and of thickening of the vein graft by a layer of fibrous tissue laid around the graft from the surrounding tissues.

Vein grafts under conditions of our experiments appear to show rather regularly an initial dilatation when placed in the aorta. In Shumacker's report,[4] the dog with an autogenous vein graft surviving 190 days showed dilatation of the graft despite the fact that it was smaller than the adjacent aorta at the time of surgery. Johnson and associates[8] have also noted that long vein grafts placed in the abdominal aorta tend to dilate. We have noted an initial dilatation in every instance. Our serial aortograms suggest that there is no further dilatation after five to six months. Whether they might dilate further with experimentally induced hypertension remains to be investigated.

The use of fascial support appears to have some merit. Pericardial tissue grafts when supported by fascia do not dilate, there is more uniform manner of endothelization, and deposition of cholesterol is reduced with the reduction in dilatation. Although autogenous venous grafts have a greater instance of success in bridging arterial defects, their dilatation when placed in major vessels would appear to be a drawback unless a fascial corset is used to prevent this complication.

CONCLUSIONS

1. Pericardial and venous grafts placed in the aorta rather regularly undergo fusiform dilatation.

2. Fascial tissue as buttress material is capable of preventing fusiform dilatation of these grafts.

3. Limited experience with dermis suggests that this also is capable of serving as suitable buttress material.

4. Autogenous pericardial, venous fascial, and dermis grafts appear to survive with minimal degenerative changes.

REFERENCES

1. Carrel, A., and Guthrie, C. C.: Uniterminal and Biterminal Venous Transplantations, Surg., Gynec. & Obst. **2**: 266, 1906.
2. Klotz, O., Permar, H. H., and Guthrie, C. C.: End Results of Arterial Transplants, Ann. Surg. **78**: 305, 1923.

3. Gross, R. E., Hurwitt, E., Brill, A. H., Jr., and Peirce, E. C.: Preliminary Observations on the Use of Human Arterial Grafts in Treatment of Certain Cardiovascular Defects, New England J. Med. **16**: 299, 1948.
4. Shumacker, H. B., Jr., Schloss, G., Freeman, L. W., Wayson, E. E., and Stahl, N. H.: Studies in Vascular Repair. Part 5. Experiments With the Use of Free Venous Transplants for Bridging Aortal Defects, Yale J. Biol. & Med. **23**: 2, 1950.
5. Swan, H., Robertson, H. T., and Johnson, M. E.: Arterial Homografts, Surg., Gynec. & Obst. **90**: 568-579, 1950.
6. Sako, Y., Clatworthy, H. W., Jr., Chisholm, T. C., and Varco, R. L.: Observations on the Fate of Pericardial and Fascial Tissue Transplanted Into the Thoracic Aorta, Presented at the Forum on Fundamental Surgical Problems, Oct. 23, 1950. To be published.
7. Carrel, A.: The Surgery of Blood Vessels, Bull. Johns Hopkins Hosp. **18**: 18-28, 1907.
8. Johnson, J., Kirby, C. K., Greifenstein, F. E., and Castillo, A.: The Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries, SURGERY **26**: 945, 1949.
9. Clatworthy, H. W., Jr., Sako, Y., Chisholm, T. C., Culmer, C. U., and Varco, R. L.: Thoracic Aortic Coarctation: Its Experimental Production in Dogs With Special Reference to Technical Methods Capable of Inducing Significant Intraluminal Stenosis, SURGERY **28**: 245-273, 1950.
10. Sperry, W., and Schoenheimer, R.: Micromethod for Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**: 745, 1934.
11. Peer, L. A., and Paddock, R.: Histologic Studies on the Fate of Deeply Implanted Dermal Grafts: Observations on Sections of Implants Buried From One Week to One Year, Arch. Surg. **34**: 268, 1937.
12. Gallie, W. E., and Le Mesurier, A. B.: Transplantation of Fibrous Tissue in the Repair of Anatomical Defects, Brit. J. Surg. **12**: 289-320, 1924.

DISCUSSION

DR. GERARD TAYLOR.—Dr. Gerbode, Dr. Herrod, and I have been following the fate of vein autografts implanted in the aortic arch and we were interested initially in two things: one, the ability of the thin-walled vein to withstand the thrust in the aortic arch immediately, and second, whether or not there would be any later dilatation of the vein graft.

In order to obtain some estimate of the relative ability of vessels to withstand internal pressures, we inflated fresh human and dog veins and arteries to the bursting point. Canine inferior venae cavae ruptured at an average pressure of 842 mm. Hg and canine carotid arteries at 1,200 mm. Hg. Human internal jugular veins required an average pressure of 1,300 mm. Hg and human carotid arteries 1,800 mm. Hg before rupture occurred. As the physiologic range of pressures is far below these figures, there seems to be no reason to believe that vein grafts would not withstand the immediate thrust on being implanted into the aorta. We also found that the apparent initial dilatation of vein grafts was due to their being of larger internal diameter than the artery into which they were implanted, and, if a vein of approximately the same diameter as the artery was selected, then no dilatation occurred.

When the vein grafts were examined after a period of months they were found to have thickened, and thus far we have not found dilatation to occur in any significant degree.

A complete aorta, bearing a 10-month-old vein graft, was removed intact and subjected to distention at varying degrees of pressure with radiopaque material. Roentgenograms were made at the various pressures and it was found that even at an internal pressure of 400 mm. Hg no dilatation of the vein graft occurred. In fact, at such high pressures the aorta above and below the graft had dilated more than the vein segment itself.

In short, we have not been able to demonstrate any dilatation in vein grafts up to ten months, and we think that if the initial size of the vein graft is chosen to match the arterial diameter, then there will be no gross dilatation at a later date.

Dr. Gerbode has in mind using an autograft of the internal jugular vein to bridge a defect in the aortic arch, if further experimental observations confirm these early results.

THE TREATMENT OF HEMORRHAGIC SHOCK WITH CORTISONE AND VITAMIN B_{12}

JOHN M. HOWARD, M.D., AND MICHAEL E. DEBAKEY, M.D., HOUSTON, TEXAS

(From the Department of Surgery, Baylor University College of Medicine)

USING the dog as the experimental animal, a standard shock preparation has been devised consisting of a slight modification[3] of the methods described by Frank, Seligman, and Fine[2] which produces an exceedingly high mortality within the first 24 to 48 hours of the experiment. Under the conditions of this controlled experiment, cortisone and vitamin B_{12} have been separately administered at various stages to the shocked animals. Their efficacy in the treatment of hemorrhagic shock has then been evaluated by comparison of the respective mortality in the treated and untreated series.

Experience has shown that certain criteria of so-called "irreversible shock" such as the amount of blood withdrawn, the duration of the shock, or the degree of hypotension are not entirely reliable. To be sure, these are all important factors in the mechanism of shock, but the individual ability of the animal to cope with these insults is so variable that they cannot be used as dependably comparable criteria of the extent of shock. For this reason the responsiveness of the individual animal to a standard degree of hypotension or his ability to cope with this insult is considered a more reliable index. Accordingly, the criterion of so-called "irreversibility" is more accurately determined by evidence of collapse of the compensatory mechanism. In this experiment the point of collapse is indicated by the inability of the shocked animal to maintain his blood pressure at the standardized hypotensive level despite repeated small transfusions of blood. Specifically, this point is met when twice within a period of 20 minutes a 25 c.c. blood transfusion fails to maintain the pressure at or above the hypotensive level of 30 mm. Hg.

THE EXPERIMENT

Under Pentothal anesthesia and using sterile technique the femoral vein and artery were cannulated bilaterally. One artery was connected to a manometer to record the blood pressure; the other artery was used to bleed the animal, the blood being collected and heparinized. One vein was used for retransfusion and the other for the gradual administration of a small amount of saline solution (15 c.c.), a vehicle for subsequent drugs. The animal was then bled to a blood pressure of 30 mm. Hg. The rate of bleeding was uniform and determined by the unrestricted flow through a large standard-size cannula. By subsequent small bleedings and later by small transfusions the pressure was maintained at 30 mm. Hg until the time was reached when twice within a period of 20 minutes a 25 c.c. transfusion failed to maintain the pressure at or above 30 mm. Hg.

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Immediately thereafter, all of the remaining collected blood was reinfused and the animal was given 300,000 units of penicillin intramuscularly. Heparin, 2.5 mg. per 100 c.c. of blood, was used as the anticoagulant.

Control Series.—Fifteen dogs were used as controls during this experiment in addition to 20 dogs in a previous study of this kind in our laboratory.[3] The shock pattern was uniform. At the completion of the experiment, with reinfusion of the remaining blood, the blood pressure would return almost to its normal level (approximately 120 mm. Hg) (Fig. 1). Periodic blood pressure

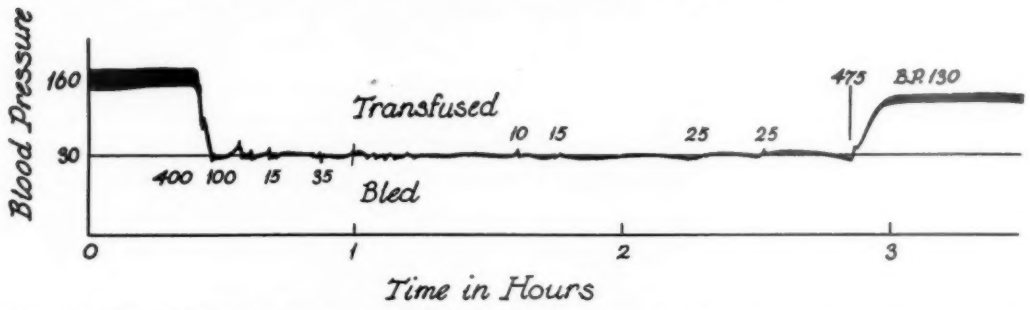

Fig. 1.—Hemorrhagic shock. Protocol of a control experiment. Note the rise in blood pressure during the final transfusion.

determinations after the completion of the experiment showed that the rise in blood pressure after retransfusion was usually transient, lasting only for several hours and gradually falling until the animal died (Fig. 2). All of the animals in this control series of 15 dogs were dead within 24 to 48 hours and 15 of the 20 dogs in the previous control series died within this period, giving a mortality of 86 per cent for the combined control series (Table I).

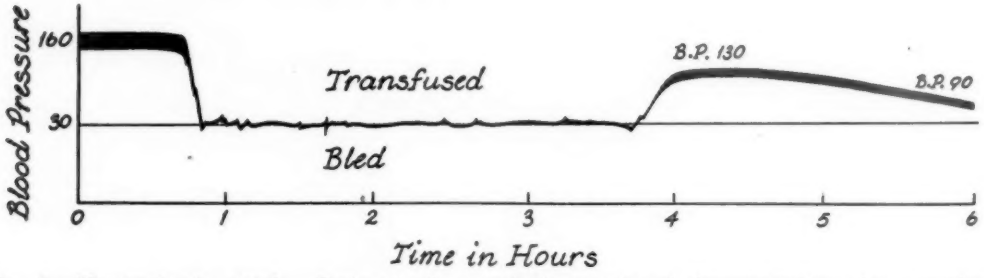

Fig. 2.—Hemorrhagic shock. Protocol of a control experiment demonstrating the secondary fall in blood pressure following the final transfusion.

Cortisone.—Because adrenal cortical secretion appears to be a physiologic response to stress, the following experiment was performed in an effort to determine the value of cortisone in carrying the animal through an otherwise fatal insult from hemorrhagic shock.

Using 50 animals, the experiment as previously described was repeated except that 50 to 200 mg. of cortisone (Cortone*) were given intramuscularly. The cortisone was administered usually as a single injection at variable times during the experiment, from 48 hours prior to the shock procedure to immediately after the retransfusion of the animal.

*Provided through the courtesy of Merck & Company, Inc., Rahway, N. J.

TABLE I. CONTROL SERIES

	NUMBER DOGS	DIED WITHIN 48 HR.	
		NUMBER	PER CENT
Controls (present series)	15	15	100
Controls (previous series)	20	15	75
Total	35	30	86

Results of Cortisone Therapy.—The 48 hour mortality for the entire treated series is 82 per cent, which appears somewhat lower than the 100 per cent for the control series in this experiment (Table II). When compared, however, with the mortality of 86 per cent for the combined control series, it is apparent that no significant difference between these series exists. It is also apparent that the cortisone had no effect whether administered before, during, or after the shock procedure (Table II). Further analysis revealed that the treated animals that lived were not exposed to shock as long nor bled as severely as those treated animals which died, suggesting that factors other than therapy may have played a role in their survival (Table III).

TABLE II. RESULTS OF CORTISONE THERAPY

TIME OF ADMINISTRATION	NUMBER DOGS	DIED WITHIN 48 HR.	
		NUMBER	PER CENT
Preoperatively	24	20	83
During shock	7	6	86
After retransfusion	19	15	79
Total	50	41	82

TABLE III. HEMORRHAGIC SHOCK; RESULTS OF CORTISONE THERAPY

	NUMBER DOGS	AVERAGE WEIGHT (KILOGRAMS)	AVERAGE TIME IN SHOCK (MIN.)	AVERAGE HEMORRHAGE PER KILOGRAM OF BODY WEIGHT (C.C.)
Controls	15	14.7	132	38.9
Treated, lived	9	15.4	95	39.1
Died	41	14.6	129	49.1

Since cortisone appears to have little or no value in altering the end results of this type of shock, the question arises as to whether or not it has any effect upon the shock pattern. This was determined by a comparison of 2 essential factors, duration of shock and extent of hemorrhage, among the animals receiving cortisone prior to shock and those not receiving it at this time. It is apparent from an analysis of the data in this respect that cortisone did not significantly alter the shock pattern (Table IV).

TABLE IV. EFFECT OF PREOPERATIVE CORTISONE ON SHOCK PATTERN

	NUMBER DOGS	AVERAGE TIME IN SHOCK (MIN.)	HEMORRHAGE PER KILOGRAM OF BODY WEIGHT (C.C.)
Preshock cortisone	22	127	43.0
No preshock cortisone	27	121	44.4

Vitamin B_{12}.—Certain observations suggested the possibility that vitamin B_{12} might have some value in this form of shock. For one thing, vitamin B_{12} is a crystalline liver substance and evidence has been presented that, at least in the experimental animal, the liver plays a significant role in the mechanism of hemorrhagic shock.[1-4] For another, vitamin B_{12} has shown promise in the treatment of anaphylatic shock.[5] For these reasons, it was considered desirable to test its efficacy in the treatment of hemorrhagic shock under the conditions of this experiment. The dosage employed is massive when compared to the therapeutic dose used in pernicious anemia.

TABLE V. RESULTS OF VITAMIN B_{12} THERAPY (900 μG.)

TIME OF ADMINISTRATION	NUMBER DOGS	DIED WITHIN 48 HR.	
		NUMBER	PER CENT
During shock procedure	21	17	81
After completing shock procedure	7	6	86
Total	28	23	82

The experiment was, therefore, repeated using 28 dogs. Each animal was given intravenously 900 μg. of vitamin B_{12} (Cobione*) in 15 c.c. saline solution. The drug was given at the rate of 75 μg. per 10 minute period either during the shock procedure or at the completion of the experiment following the retransfusion. It was found that if the drug was given rapidly a fall in blood pressure occurred, so that in order to avoid influencing the criteria for terminating the experiment 7 animals were given the drug only at the completion of the shock procedure.

TABLE VI. HEMORRHAGIC SHOCK; RESULTS OF VITAMIN B_{12} THERAPY

	NUMBER DOGS	AVERAGE WEIGHT (KILOGRAMS)	AVERAGE TIME IN SHOCK (MIN.)	AVERAGE HEMORRHAGE PER KILOGRAM OF BODY WEIGHT (C.C.)
Controls	15	14.7	132	38.9
Treated, lived	5	17.3	112	54.7
Died	23	15.9	119	45.2

Results of Vitamin B_{12} Therapy.—A comparison of the 48 hour mortality among the animals receiving vitamin B_{12} during the shock procedure with the mortality of those receiving the drug after completion of the experiment revealed no significant differences (Table V). Further analysis of the data showed that the shock pattern as reflected by the duration of shock and the extent of

TABLE VII

	NUMBER DOGS	DIED WITHIN 48 HR.	
		NUMBER	PER CENT
Controls	35	30	86
Cortisone	50	41	82
Vitamin B_{12}	28	23	82

*Provided through the courtesy of Merck & Company, Inc., Rahway, N. J.

hemorrhage was not significantly altered among the treated animals that lived and those that died (Table VI). It is also apparent that the mortality among the treated animals is not significantly different from that of the controls, the respective figures being 82 per cent and 86 per cent (Table VII).

SUMMARY

1. A method of producing a highly lethal form of hemorrhagic shock is described. This consists essentially in bleeding the animal until the systolic pressure reaches 30 mm. Hg and maintaining it at this level by subsequent small bleedings or reinfusion of blood until a specific criterion of collapse of the compensatory mechanism is evident. This criterion is met when twice within a period of 20 minutes a 25 c.c. blood transfusion fails to maintain the pressure at or above 30 mm. Hg. In the combined control series of animals this type of hemorrhagic shock produced a mortality of 86 per cent (Table VII).

2. Using 50 dogs the experiment was repeated except that 50 to 200 mg. of cortisone were given intramuscularly before, during, or after the completion of the experiment. Eighty-two per cent of the animals so treated died within 48 hours and only 10 per cent of the animals completely recovered from the experiment (Table VII).

3. An additional 28 dogs were used in a similar experiment to test the efficacy of vitamin B_{12} in the treatment of this type of hemorrhagic shock. Eighty-two per cent of the animals so treated died within 48 hours and 18 per cent recovered from the experiment (Table VII).

4. The shock pattern as reflected by duration of shock and extent of hemorrhage was not significantly altered by either cortisone or vitamin B_{12}.

5. These results, therefore, indicate that neither cortisone nor vitamin B_{12} has any significant effect upon the course of hemorrhagic shock under the conditions of this experiment.

REFERENCES

1. Fine, J., Seligman, A. M., and Frank, H. A.: On the Specific Role of the Liver in Hemorrhagic Shock, Ann. Surg. **126**: 1002, 1947.
2. Frank, H. A., Seligman, A. M., and Fine, J.: Traumatic Shock, XIII. The Prevention of Irreversibility in Hemorrhagic Shock by Viviperfusion of the Liver, J. Clin. Investigation **25**: 22, 1946.
3. Hay, Elliott B.: The Effect of Intravenous Sodium Dehydrocholate on the Mortality Rate Following Hemorrhagic Shock, SURGERY **29**: 829, 1951.
4. Seligman, A. M., Frank, H. A., and Fine, J.: Hemorrhagic Shock Treated by Viviperfusion of the Liver, J. Clin. Investigation **26**: 530, 1947.
5. Traina, V.: Vitamin B_{12} as an Antianaphylactic, Nature **166**: 78, 1950.

THE CLOSURE OF THE ABDOMINAL INCISION: A COMPARISON OF MASS CLOSURE WITH WIRE AND LAYER CLOSURE WITH SILK

STANLEY O. HOERR, M.D., CLEVELAND, OHIO, ROBERT ALLEN, M.D., KANSAS CITY, MO., AND KENNETH ALLEN, M.D., BURLINGAME, CALIF.

(From the Cleveland Clinic Foundation and the Bunts Educational Institute)

A RICH literature upon the subject of the placing, making, and closing of the abdominal incision attests to the many methods which surgeons have employed. The existing variations in technique are evidence that no one method is so pre-eminently superior that its advantages will force every surgeon to adopt it at the expense of abandoning a more familiar method. End results must be very similar or less effective techniques would have been abandoned years ago. And yet it is amazing how experienced surgeons become partial to their particular system, and how few controlled comparisons have been reported in human patients.

Accumulating experience has seemed nevertheless to establish certain principles: (1) accurate approximation is essential; (2) suture material should be as fine as is consistent with safety; (3) suture material should be kept at a minimum; (4) nonabsorbable suture material produces less inflammatory and foreign body reaction in a wound, but may act as an unpleasant nidus of minor sepsis at a later date, particularly in a potentially infected wound.

The senior author was taught to close wounds by approximating individual layers with interrupted sutures of fine silk. This produces in general a very satisfactory wound, although an occasional wound may "spit" silk, even in the absence of frank sepsis. In long incisions it may be a rather time-consuming procedure, and in an obese patient with poor abdominal relaxation it may even become extremely difficult to execute. But the reactionless wound which usually results had seemed to be well worth the effort. On the other hand, the "mass closure" with stainless steel wire, in which peritoneum, muscle, and fascia were closed with large interrupted sutures, seemed on the face of it anatomically unsound and physiologically undesirable. A comparison of these 2 methods was undertaken because of the admitted simplicity of the steel wire closure, and because a cursory inspection of a number of wounds closed in this manner by a colleague appeared to disclose no more induration or inflammatory response than that occurring in the average wound closed with interrupted silk.

MATERIAL AND METHODS

Selection of Wounds and Technique.—For the 6 months from Jan. 1, 1950, through June 30, 1950, all abdominal wounds were closed alternately by the interrupted silk technique (Fig. 1) and by the "mass closure" with interrupted No. 31 stainless steel wire (Fig. 2). The silk closure

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was a variation of the technique given by Cutler and Zollinger,[1] and the technique for the wire closure was essentially that of Jones and associates.[2] A series of 127 wounds in 122 patients resulted; 66 were closed with the wire technique, and 61 with the silk technique. Inguinal and femoral herniorrhaphies were not included in the study, nor was the so-called McBurney incision. In several instances strict alternation was interrupted by the use of the wire closure because of its comparative speed in a patient subjected to an unusually long procedure; and patients who had a second operation were closed by the same method used the first time.

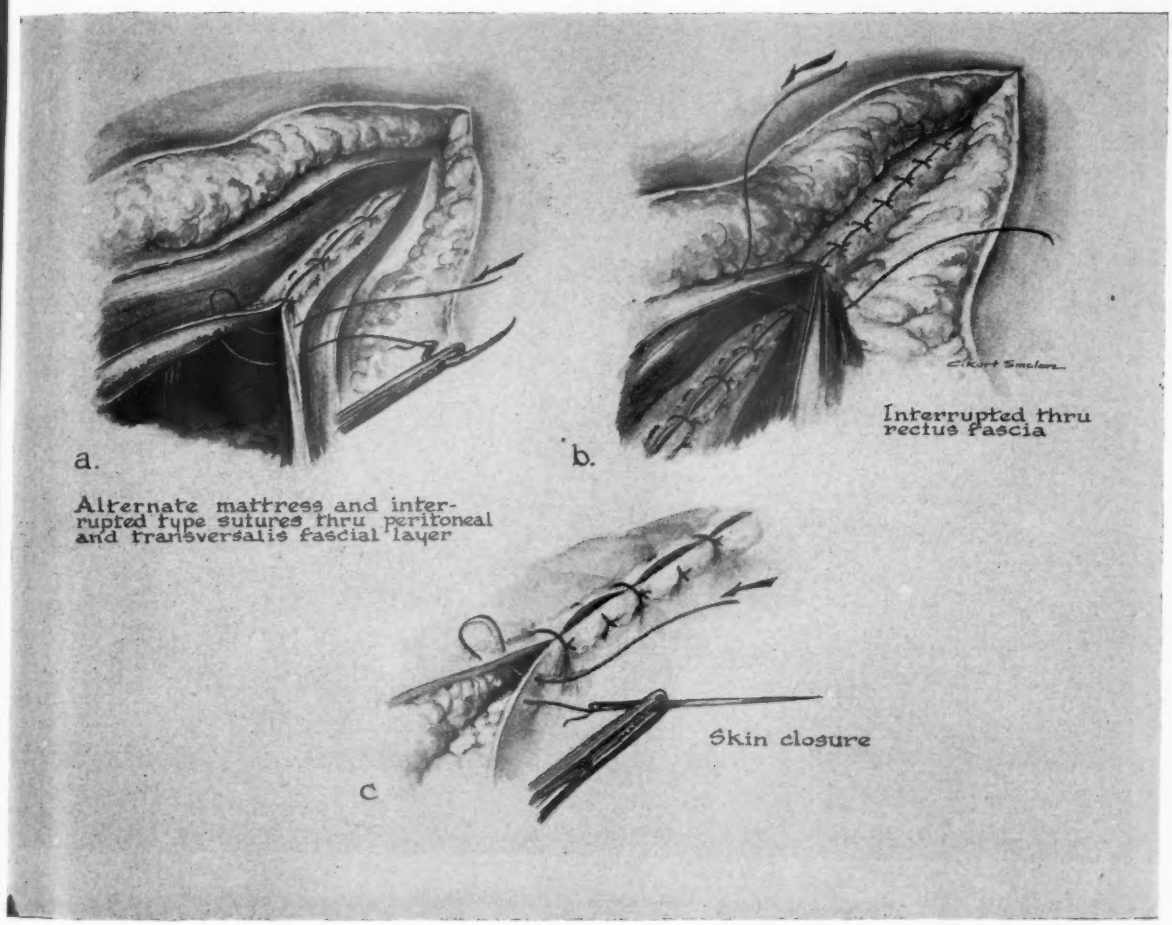

Fig. 1.—Silk technique.

The bulk of the operative procedures were of a major character involving exploration or resection of stomach or colon, vagus resection with gastroenterostomy, cholecystectomy and exploration of the common bile duct, and total hysterectomy. Ninety per cent of the incisions exceeded 15 cm. in length.

Each closure was performed by one of the three authors, and a uniform technique in opening the wound and protecting it from possible contamination was employed. Bleeding vessels in the fat were ligated with 000 silk. After

gastrointestinal anastomoses, gloves were changed prior to wound closure. The length and depth of the wound were measured with a sterile metal rule, and an accurate notation made as to the total duration of the operation and of the closure. Muscle was not approximated, a few silk sutures were taken in subcutaneous fat in obese patients, and the skin closed with silk sutures in the silk closures and with metal clips in the wire closures. Retention sutures were not employed. No emphasis whatsoever was placed on speed, the only aim with either method being a sound closure.

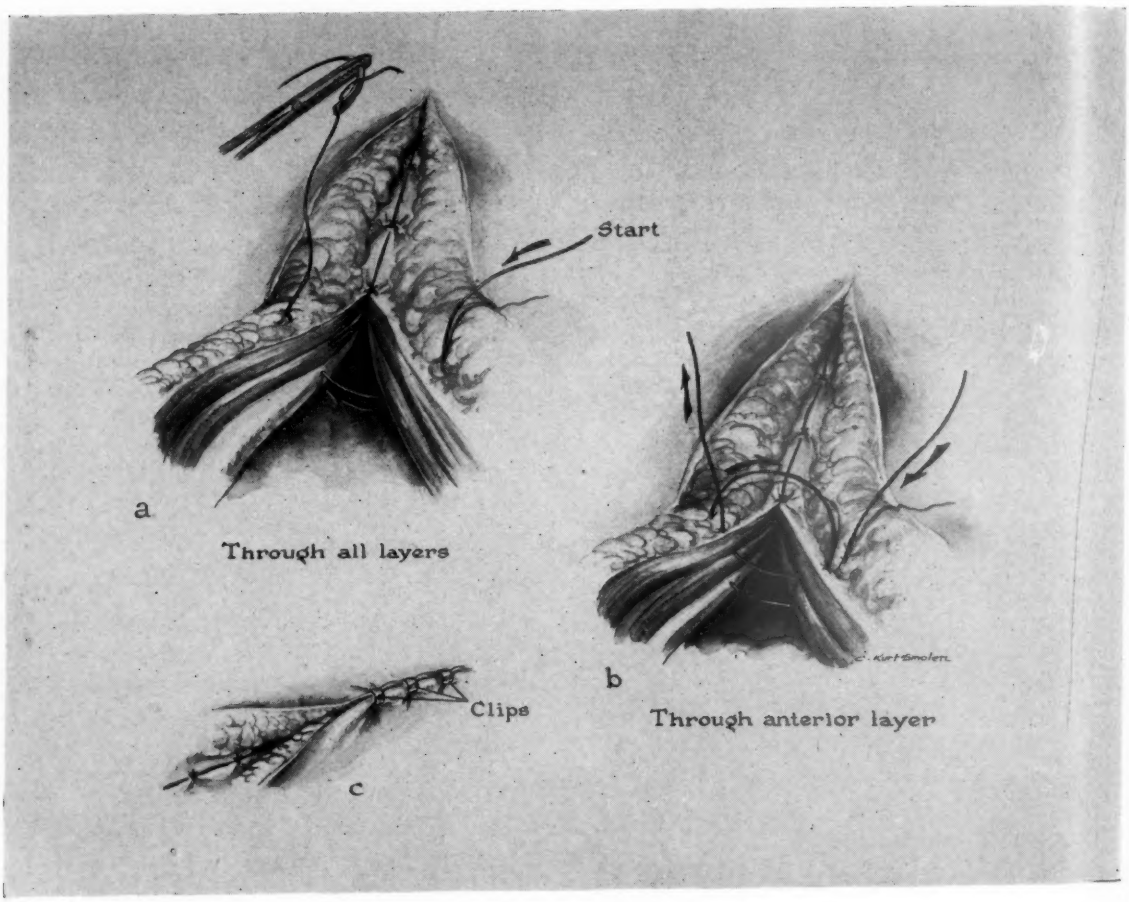

Fig. 2.—Wire technique.

Postoperatively, wounds were closely scrutinized for all complications, which were duly recorded. Discharge from a drain site has not been included. Wounds were dressed only at the time sutures or clips were to be removed or if wound sepsis was suspected. Silk sutures in the skin were removed on the fifth to seventh day, and metal clips were usually loosened on the second or third day and removed on the fifth or sixth day. An accurate record was kept of the doses of narcotics which each patient required, and in addition, an estimate was made as to how much pain the wound had caused the patient.

Factors Affecting Healing.—Although the series is small, the 2 groups of closures appear to be roughly comparable by all ordinary standards. In Table

TABLE I. TYPE OF INCISION

	WIRE	SILK
Vertical upper abdomen	39	31
Vertical lower abdomen	11	8
Subcostal	7	8
Transverse	9	14
Total	66	61

I, the various types of incision are seen to be about equally represented in the silk closure and in the wire closure. In Table II, the potential contamination of the wound is arbitrarily rated from "clean" to "pus." A cholecystectomy, for example, is "clean" (even if incidental appendectomy is performed) unless the common duct is explored, when it is listed under "bile." If both stomach and colon were opened, the wound is placed under the contamination rated the

TABLE II. POTENTIAL CONTAMINATION AT OPERATION

	WIRE	SILK
Clean wound	19	20
Vaginal vault	7	11
Bile	3	4
Urine	1	0
Open upper gastrointestinal tract	26	16
Open ileum	2	1
Open colon	5	4
Inflammatory mass	2	4
Pus	1	1
Total	66	61

more severe, "open colon." "Inflammatory mass" includes such conditions as a gangrenous gall bladder or appendix without frank pus. The distribution is fairly uniform, with perhaps a slight advantage for the silk closure. Since the longer a wound is open, the more it is exposed to air-borne contamination, Table III lists the operations by their total length, and again there is very little to choose between the 2 groups.

TABLE III. TOTAL DURATION OF OPERATION

TIME	WIRE	SILK
1 hr. or less	10	7
1 - 1½ hr.	21	23
1½ - 2 hr.	14	19
2 - 2½ hr.	8	7
More than 2½ hr.	13	5
Total	66	61

RESULTS

Early Wound Complications.—The complications listed in Table IV were noted in the hospital. There were 4 infections in wire wounds and 3 in silk wounds. In spite of the fact that many of the operations were for advanced cancer in debilitated patients, there was no evisceration in the series. A dehiscence of skin and fat occurred in an extremely obese patient whose wound was closed by wire, when the metal skin clips were inadvertently removed on the third postoperative day.

TABLE IV. EARLY WOUND COMPLICATIONS

	WIRE	SILK
Infection	4	3
Superficial dehiscence	1	0
Skin malapproximation	4	2
Ecchymosis or hemorrhage	2	3

There was only 1 infection in a clean wound; the closure was with silk and the infection minimal. The 6 other infections occurred in wounds with varying degrees of potential contamination and 2 of these were trivial. Two occurred in patients who needed secondary operations, and 1 occurred in a debilitated patient with intestinal obstruction requiring an ileal anastomosis. It is unlikely that suture material played a role in any of these early infections.

Skin malapproximation is usually a result of carelessness and is more likely to occur with metal clips. Two of the patients who bled from the wound had a blood dyscrasia.

Wound Pain.—The pain which a patient experiences following an abdominal operation is thought to be in most instances from the incision itself. Occasionally the underlying disease will play a role, and the presence of peritonitis or ileus undoubtedly increases discomfort. Transverse or oblique incisions are generally believed to give less discomfort than vertical incisions, and incisions in the upper abdomen cause more pain than those in the lower abdomen. The "pain threshold" of the patient also plays a very important part. With due regard for all these variables, an attempt was made to determine whether there was a measurable difference in the pain caused by a silk wound and that caused by a wire wound. This was done in 2 ways (each admittedly of limited value): by counting the doses of a narcotic which each patient received in the first 48 hours after operation, and by recording an estimate—from 1 plus to 4 plus—of the amount of pain which the surgeon thought that the patient had experienced. By either method no distinction could be found between the two types of closure.

Comparative Speed of Closure.—It was to be expected that the mass closure with wire could be done more rapidly than the closure with interrupted silk, since it requires far fewer sutures. This was proved to be the case, as demonstrated in Tables V and VI. The total duration of the closure is analyzed for the 2 groups in Table V; for an average incision this results in a time savings of only 5 minutes for the wire closure, since the median time consumed in a wire closure was 20 minutes and in a silk closure, 25 minutes. The longer the incision, however, the more pronounced becomes the difference. In Table VI

TABLE V. DURATION OF CLOSURE

MINUTES	WIRE	SILK
15 or less	16	6
16 - 20	21	7
21 - 25	13	19
26 - 30	10	17
31 or more	6	12

Median time: wire, 20 minutes; silk, 25 minutes.

TABLE VI. WOUND SIZE AND DURATION OF CLOSURE*

INCISION DEPTH (CM.)	MEDIAN TIME (MIN.)	
	WIRE	SILK
2	1.0	1.3
3	1.0	1.3
4	1.0	1.3
5	1.0	1.5
All wounds	1.0	1.3

*Minutes required per centimeter of length of wound.

incisions are grouped as to depth, and the rate of closure calculated according to the length of the incision. The rate is figured by dividing the time of the closure in minutes by the length of the incision in centimeters, resulting in the minutes required per centimeter of wound length. It can be seen that the results are remarkably constant, being 1.0 minute per centimeter for a wire closure and 1.3 minutes per centimeter for silk. An unexpected finding was the fact that in this series the depth of the wound did not appear to have any appreciable influence. In addition, it was the opinion of each of the authors that in a closure rendered difficult by reason of obesity or poor abdominal relaxation, the wire closure was more easily effected and was also more secure, since the rectus fascia is pierced twice with each wire suture, thus halving the chance of either missing the fascia completely or of having the suture tear out.

Late Wound Complications.—Every effort was made to see each wound at a period of 6 months or longer after the operation. The actual follow-up is presented in Table VII. Although it is neither a perfect follow-up nor sufficiently long, it is believed that it gives a fair index of what may be expected. The patients listed as dead were for the most part explored for hopeless disease and died within a few weeks or months after operation; the wound was presumably satisfactory for this period of time. A follow-up by letter is not a reliable index of trouble, since 2 of the patients who had small hernias were not aware of it. On the other hand, many of the patients live at a distance from the Clinic, and no other means of checking is available; several of these patients mentioned painful incisions or small abscesses (presumably from suture material).

TABLE VII. FOLLOW-UP DATA

	WIRE	SILK
Patient dead	10	6
No follow-up	1	3
1 - 2 mo.	4	2
3 - 5 mo.	4	7
6 - 12 mo.	47	43

By letter or phone: wire, 14; silk, 11.

Table VIII lists the late complications. The one hernia in a wire closure occurred in the previously mentioned obese patient who had the superficial dehiscence. A wound infection followed an attempt at secondary closure, and ultimately a large hernia developed. One hernia in a silk wound occurred in the patient who had a wound infection following a transcolonic polypectomy.

TABLE VIII. LATE WOUND COMPLICATIONS

	WIRE	SILK
Hernia	1	3
Minor sepsis	2	6
Pain	3*	4
Keloid	4	3

*One wire suture removed.

The other 2 hernias in silk wounds occurred in upper abdominal midline incisions, after gastric resection, and are small ones at the time of writing; one of these 2 wounds had had a small postoperative infection.

Keloid and pain in the wound are about equally divided between silk and wire closures, but 6 patients in the silk group developed late minor infections or sinuses related to suture material after the wound had been pronounced perfectly healed. One patient required the removal of a wire suture.

COMMENT

The study indicates that there is little to choose between the abdominal incision closed with the wire technique and that closed with interrupted silk in so far as immediate postoperative complications and postoperative pain are concerned. As a rule, both types of wounds have a minimum of reaction. The wire closure is technically simpler and requires only about three-fourths as much time to perform as the silk closure. In the available follow-up, it would seem that silk closures are followed by a higher incidence of unpleasant sequelae as a late development. It is not yet possible to state that the incidence of hernia will be less in the wire wounds, although the fact that the wire forms a permanent internal retention suture would lead one to expect this outcome.

It is not advocated that a wire closure be done in every case. The authors feel that in short wounds in thin patients who have "clean" operations, a silk closure may be preferable, since it is thin patients who occasionally complain of a sticking sensation or who feel a small lump under the skin from a wire suture.

Either the silk or the wire technique requires practice for proper execution. In the wire closure, care must be exercised to avoid injury to bowel by a careless piercing with the large needle, or by pinching when the suture is tied. The bowel may be protected with a ribbon retractor or a flexible rubber visceral retractor; the wire sutures should be tied as placed except for the last 2 or 3, and the peritoneal surface of the wound palpated from time to time.

SUMMARY

1. A series of 127 abdominal incisions in 122 patients were alternately closed by a method employing No. 31 stainless steel wire as interrupted sutures through peritoneum, muscle, and rectus fascia, and by a layer-to-layer technique with interrupted sutures of 00 silk. The skin was closed with metal clips in the wire wounds, and with interrupted silk in the silk wounds.

2. The group of 66 wire closures and the group of 61 silk closures were roughly equivalent from the standpoint of location of incision, length of in-

cision, duration of operative procedure, and potential contamination at the time of operation.

3. There was roughly the same incidence of early postoperative complication in the two groups of wounds. There was no detectable difference in the appearance of the wounds, and postoperative pain was the same.

4. In the available follow-up late complications appeared to be about the same with the exception of minor infections or sinuses which occurred more frequently after a closure with interrupted silk. There have also been 3 hernias in silk wounds to 1 in a wire wound.

5. Wire closures are simpler to execute, require only three-fourths as much time as a silk closure, and seem to be especially well adapted for use in obese patients with long incisions.

REFERENCES

1. Cutler, E. C., and Zollinger, R. M.: Atlas of Surgical Operations, ed. 2, New York, 1949, The Macmillan Company.
2. Jones, T. E., Newell, E. T., Jr., and Brubaker, R. E.: The Use of Alloy Steel Wire in the Closure of Abdominal Wounds, Surg., Gynec. & Obst. 72: 1056, 1941.

DISCUSSION

DR. DERYL HART.—Recently we have attacked the problem of preventing evisceration by the use of wire sutures running straight through the abdominal wall from side to side and passing just anterior to the peritoneum at the suture line. These bear all tension on metal plates placed laterally at either end of the straight wire sutures. The plates are about 1 to 1½ inches square so as to conform to the body contour and have 2 holes through which the sutures are passed and twisted so as to approximate the fascia without tension except on the wires. The layers of the abdominal wall can be approximated with any suture material desired since they are used for approximation and not for tension. These wire sutures are used only on the patient in a poor state of nutrition and are inserted by a very long straight needle. No evisceration has occurred in patients so closed and the patients are far more comfortable.

DR. STANLEY O. HOERR (Closing).—I have pointed out that we had no evisceration in the series which we reported, nor to the best of my knowledge was there any evisceration in over 1,000 abdominal wounds closed by this technique in the past year at the Cleveland Clinic. Retention sutures were not used in any of the incisions whether closed by wire or by silk.

SMALL BOWEL OBSTRUCTION FOLLOWING COMBINED ABDOMINOPERINEAL RESECTION OF THE RECTUM

HOWARD ULFELDER, M.D.,* AND WILLIAM C. QUINBY, JR., M.D.,** BOSTON, MASS.

THE motive for this study grew out of a clinical impression that of the various forms of gastrointestinal dysfunction which follow the Miles operation, mechanical small bowel obstruction is fairly frequent and always serious. Since the operation is now part of the technical armamentarium of the resident staff in many hospitals, the corollary was to review a group of ward cases so that the findings would represent a variety of experience and the conclusions be generally applicable.

The gist of this communication may be stated very simply. It will demonstrate that mechanical small bowel obstruction complicates recovery from combined abdominoperineal resection of the rectum in 8 per cent of cases and is the cause of death in 2.8 per cent in our series. It will show further that the diagnosis should be obvious in the majority of instances and that the proper treatment is early exploration.

MATERIAL

The material for this analysis consists of 249 consecutive patients in whom one-stage removal of the rectum and lower sigmoid colon was performed on the wards of the Massachusetts General Hospital during the 10 years 1940 through 1949. Although patients who had a preliminary cecostomy are included, we have excluded anyone in whom complete diversion of the fecal stream was done prior to the resection.

Sixteen patients developed symptoms unquestionably due to small bowel obstruction, with anatomic proof in 10 of them. In 4 others the complication was almost a certainty, although not so clearly documented. Thus, 8 per cent of our patients developed symptoms and signs sufficiently clear to permit this diagnosis in retrospect.

The mortality of the series as a whole was 6 per cent (15 patients). Unrelieved small bowel obstruction was present in 7 of these cases, and it was the direct cause of death in 5, strangulation and gangrene of the bowel having developed in 2 instances. Therefore, complication of recovery in 8 per cent of our patients and death in 2.8 per cent of them may be attributed to small bowel obstruction.

PREDISPOSING CAUSES

Three features of the operation were considered most likely to be involved in this complication: (1) the new peritoneal floor, (2) the gutter lateral to the colostomy on the left, and (3) the abdominal incision with the sigmoid colon fixed within it. Each was occasionally responsible for obstruction, but rarely

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*Assistant Surgeon, Massachusetts General Hospital; Clinical Associate in Gynecology, Harvard Medical School.

**Assistant in Surgery, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

could this be anticipated by the surgeon at the time of operation. In most patients the left gutter was closed, although a few operators deliberately omitted this step. Obstruction was twice discovered to be due to prolapse of small bowel down this gutter; in both cases closure had been done but had apparently separated. Incarceration of bowel in holes in the new pelvic floor was proved to have caused obstruction in 5 patients, but in 3 of these the closure at the time of operation appeared to be completely satisfactory.

These points of danger have been described by many surgeons, notably Gabriel[3, 4] and Hayden,[5] with recommendations for prevention and therapy. Our study does not divert emphasis from the technical principles of careful peritoneal approximation and closure of small foramina of the left gutter, but it does indicate that no technique is infallible.

DIAGNOSIS

In every case of the 16 patients we consider certain to have been obstructed, the onset was sufficiently abrupt to elicit comment in the record. The symptoms were classical: cramps followed by nausea, vomiting, and distention. Peristalsis was always present, usually active but rarely high-pitched or with rushes. Complete cessation of colostomy function was rare. Flat film of the abdomen always showed dilated small bowel loops. Occasionally gas was also seen in the colon, but never with distention of this portion of the bowel. Thin barium was injected through the long intestinal tube after it ceased to advance in a few patients, and several times demonstrated points of persistent, incomplete obstruction. In the 2 patients in whom gangrene, perforation, and peritonitis developed the physical findings changed accordingly.

In the 4 additional cases where obstruction is considered very probable, the findings were similar but less marked or less prolonged. A few other patients showed transient interference with bowel function, insufficient to justify including them in this category, but possible instances nonetheless.

Considering the 20 patients with obstruction as a group, a definite period of uncomplicated recovery from the initial operation can be traced in 12, while the other 8 developed their symptoms earlier. Our patients showed a predilection for getting into trouble on the sixth or seventh day, and we are interested to note that Gabriel[4] reported a similar tendency in his series. Wound sepsis, colostomy malfunction, age of patients, and associated physiologic changes all conspired to cloud the issue as far as diagnosis goes. It is fair to state, however, that the presence of obstruction was strongly suspected in most cases and the decision deliberately made to carry the patients on intestinal intubation and parenteral feeding with the hope of spontaneous recovery.

TREATMENT

Table I shows that nonoperative therapy resulted in recovery in 10 of the 20 obstructed patients. In the majority of those who recovered, improvement in signs and symptoms was noted within 48 hours of the institution of treatment.

TABLE I. RESULTS OF THERAPY IN TWENTY CASES OF OBSTRUCTION

	RAPID RECOVERY	SLOW RECOVERY	DIED	TOTAL
Nonoperative	8	2	3	13
Intubation and operation	2	1	4	7
Total	10	3	7	20

However, the fact that suction of 17 and 18 days' duration was necessary in 2 cases suggests that there was undue risk of losing these patients from starvation even after strangulation had been virtually excluded.

Of the remaining 10, 3 improved without operation, but died in from 2 to 4 weeks, either because obstruction was incompletely relieved or because they were unable to overcome the severe depletion.

Seven patients had exploratory operation and 3 recovered despite 6 days or longer of preliminary intestinal intubation. The 4 who died were in desperate straits by the time surgery was offered.

DISCUSSION

The hazard of the Miles operation has been greatly reduced over the course of the past 15 years, primarily because the complications of sepsis and shock have almost been eliminated. With these have also disappeared the major causes of paralytic ileus. The net effect of this improved situation has been to bring other complications into greater prominence. One may expect future reductions in morbidity and mortality only if these are individually scrutinized with the intention of eliminating their causes or of instituting proper treatment early in their courses. The papers of Miles, Gabriel, Jones, and Hayden indicate that small bowel obstruction has always contributed to the morbidity and mortality. Even the recent series of Binkley and Deddish[7] shows nearly 6 per cent incidence of postoperative obstruction.

Small bowel obstruction in these patients is usually secondary to adherence of intestine to raw surfaces or to separation of the peritoneal closure in the pelvis or left gutter. Although care must be exercised in the selection of suture material and placement of the sutures, a constant effort must be made to reduce the tension to which these closures are exposed. This demands re-evaluation of many factors in the postoperative care of these patients, including the use of intestinal tubes to prevent distention, the handling of the posterior wound and its packs or drains, the interval between operation and resumption of the semierect posture by the patient, the type of diet exhibited, and the manipulation to which the colostomy is subjected.

The surgeon must be alert to the possibility of obstruction. His interpretation of signs, symptoms, and x-ray findings should not be influenced by the consideration of normal postoperative ileus and malfunction of the colostomy stoma, nor by reluctance to subject his patient to another abdominal operation. Small bowel obstruction in these patients is as dangerous as the mechanical obstruction one sees developing acutely in any individual with a previous laparotomy. It is an exception to the rule that obstruction appearing in the immediate

postoperative phase can safely be managed by intubation and watchful waiting. Our study has shown that this policy is attended with a staggering mortality. We must conclude that intubation and parenteral therapy in these individuals should be routinely instituted as a prelude to exploration, and that surgery should be withheld only in cases where evidence of recovery is prompt and unequivocal.

SUMMARY

1. The records of 249 patients subjected to Miles resection at the Massachusetts General Hospital have been reviewed.

2. The hospital mortality was 6 per cent (15 patients).

3. Small bowel obstruction developed in 8 per cent (20 patients) with a mortality of 2.8 per cent (7 patients).

4. Nonoperative therapy resulted in recovery in only 10 individuals.

5. Herniation of bowel through the new pelvic floor or down the left gutter was the usual mechanism of obstruction.

6. A period of uncomplicated recovery often precedes the onset of acute obstruction.

7. We conclude that exploratory operation is strongly indicated when intestinal intubation does not provide prompt relief of all symptoms.

REFERENCES

1. Jones, D. F.: Carcinoma of the Rectum, Boston M. & S. J. **159**: 707, 1913.
2. Jones, D. F.: End Results of Carcinoma of the Rectum, Ann. Surg. **90**: 677, 1929.
3. Gabriel, W. B.: Five Cases of Small-Gut Obstruction Round Colostomies, Proc. Roy. Soc. Med. (Sect. Surg., Sub-Sect. Proct.) **21**: 47, 1928.
4. Gabriel, W. B.: Principles and Practice of Rectal Surgery, Springfield, Ill., 1948, Charles C Thomas, Publisher.
5. Hayden, E. P.: Rectum and Colon, Philadelphia, 1939, Lea & Febiger, p. 382.
6. Miles, W. E.: A Method of Performing Abdomino-Perineal Excision for Carcinoma of the Rectum and of the Terminal Portion of the Pelvic Colon, Lancet **2**: 1812, 1908.
7. Binkley, G. E., and Deddish, M. R.: Complications of Abdominoperineal Resection of Rectum for Cancer, New York State J. Med. **47**: 2547, 1947.

PECTUS EXCAVATUM AND HEART FAILURE

MARK M. RAVITCH, M.D., BALTIMORE, MD.

(From the Department of Surgery of The Johns Hopkins University and The Johns Hopkins Hospital)

PECTUS excavatum (funnel chest, trichterbrust) is a congenital anomaly in which the body of the sternum is depressed to form a concavity which may reach to the vertebral bodies or, passing to one side, into the paravertebral gutter. The lower costal cartilages on either side bend dorsally toward the displaced sternum, giving breadth to the concavity, the depth of which is usually maximal just above the xiphisternal junction. The deformity is commonly noted soon after birth, but the feature of greatest importance is the tendency to progression. The degree and rate of progression are variable and inconstant. We have seen a number of infants in whom the deformity was unnoticed at birth only to become progressively more severe in the months after it first became obvious. Older patients occasionally claim the deformity was inconspicuous until early adolescence. The frequent familial incidence of the condition is well established. Sainsbury[1] has reported a family in which 6 cases of funnel chest occurred in lineal descent in 4 generations without consanguineous marriages. More often the same deformity is seen as a sporadic, isolated phenomenon.

The cause of the deformity is not well established. Shortening or contracture of the central tendon of the diaphragm drawing the sternum inward is ascribed as the cause by Brown,[2] among contemporary writers, and strongly seconded by Lester,[3] who with him emphasizes the importance of a substernal ligament. Sweet[4] suggests that an overgrowth of the ribs may be responsible. This latter theory was first advanced in 1873 by Flesch,[5] then a medical student at Frankfurt. In many respects, the theory of production of the deformity by overgrowth in the length of the ribs is the most attractive. At all events the condition frequently occurs in otherwise well children and independent of any history of scurvy or rickets or of respiratory obstruction.

The most obvious results of the deformity are seen in the general habitus of the patients, in their posture and in the configuration of the thorax. In infancy there is noted chiefly the sternal hollow exaggerated on inspiration. All of these patients when young and before the ribs are fixed demonstrate paradoxical respiratory movement of the sternum, which sucks in with inspiration often to an astonishing degree. Along with the motion of the sternum, there is usually a prominent protrusion of the abdomen on inspiration. As the children grow they develop thin, flat chests and a mild dorsal kyphos and carry their heads thrust forward. They tend to be tall and thin, flat-chested, and round-shouldered.

In some instances the heart is compressed between the spine and the sternum, but more often the depression of the sternum displaces the heart to the left, even in the less severe cases. In the more severe deformities, the heart is displaced far to the left and rotated posteriorly. Pushed out in the left hemi-

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thorax, in a patient with a thin, flat chest, the heart gives the impression of being imprisoned in the flattened chest between the anterior and posterior parietes—and, in fact, it may be so imprisoned. Such a degree of deformity does not often develop before adolescence and it is not possible to predict which infant with pectus excavatum will go on to develop a severe deformity and which will not.

The older children are frequently conscious of their deformities, and, especially in the case of boys, suffer a good deal of teasing from their playmates. It is in the older children too that there often occurs, after operative correction, the sudden discovery of increased exercise tolerance, although it had not been appreciated before that any limitation of exercise tolerance existed.

While severe cardiac embarrassment is rare, many patients have symptomatic limitation of exercise tolerance attributable to their deformities and occasionally very severe cardiac disorders occur. The occurrence of symptomatic cardiac disturbances due to this deformity is still occasionally disputed, although there is now an adequate accumulation of evidence to show that cardiac disturbances are not at all rare in association with funnel chest. It may be of interest to cite the recorded experience with pectus excavatum and cardiac disorders.

Sauerbruch's first patient,[6] operated upon in 1913, the report of which opened the era of surgical treatment of trichterbrust, was an 18-year-old boy with dyspnea and intolerance for even mild exercise. With the slightest exertion he would develop violent palpitation and a feeling of pressure so that he could not work. The pulse was irregular, and severe dyspnea and extreme irregularity of the heartbeat followed slight exertion. Three years after Sauerbruch's operation (resection of the fifth to ninth left costal cartilages and the corresponding portion of the left side of the sternum) the pulse was perfectly regular and the patient could work 12 to 14 hours a day without difficulty.

Sauerbruch's second patient,[7] 18 years after his first, was a young girl with severe funnel chest and marked phenomena of cardiac displacement. In this patient he divided the costal cartilages on both sides and elevated the sternum by traction on a wire passed behind it. The result was ultimately good and all symptoms were relieved.

Hoffmeister[8] reported the case operated upon by Lexer. The patient was a 19-year-old boy with a congenital trichterbrust and a 2-year history of precordial pain, exertional dyspnea, and palpitation. The heart was displaced to the left. Operation (removal of the sternum and fifth to ninth costal cartilages on both sides) brought a great measure of relief. Lexer had planned to replace the sternum and is sometimes thought to have done so, but Hoffmeister stated that the thorax spread and the gap was too wide to retain the sternum. There remained slight exertional dyspnea but the precordial pain and palpitation were gone and the heart returned to a normal position.

Alexander (1931)[9] reported 2 cases. The first patient was a 16-year-old boy alleged to have injured the sternum in wrestling 4 years before. The

deformity appeared gradually in association with pain, dyspnea, and some dysphagia. Operation (division of 5 costal cartilages on each side, a T sternotomy, and skeletal traction on the sternum) relieved all his symptoms.

His second patient was a 20-year-old girl with a sternum depressed after an automobile accident. She had severe precordial pain, dyspnea, and palpitation, with some relief from operation.

Carr's (1933)[10] first patient, a 19-year-old girl, complained of faintness, dyspnea upon exertion, and rapid cardiac action. She was once diagnosed as having mitral disease and twice was discharged from a nurses' training school on account of her poor health. There was a slight systolic precordial murmur (a regular finding in these patients). The rhythm was regular. An electrocardiogram showed a diphasic T wave in Lead II, negative T in Lead III. The heart was displaced to the left by a fairly marked funnel chest. Four months after operation* (Lexer type operation with resection of sternum and cartilages) the murmur was audible in only a very small area, cardiac consciousness was gone, and she could walk a mile or more a day. Carr's second patient, a 13-year-old boy with a deep funnel chest, cyanosis, and moderate dyspnea, was not operated upon.

Edeiken and Wolferth (1932)[11] studied 10 patients with funnel chest. One 33-year-old man had an uncomplicated case with history of paroxysmal auricular fibrillation of 8 years' duration. The electrocardiograms were thought not to show definite abnormalities attributed to the funnel chest. In most cases the heart was displaced, usually to the left and upward.

Ochsner and DeBakey (1938),[12] in their exhaustive review, reported a 21-year-old woman with a severe deformity who had a sensation of tightness and constriction in the chest, a constant, dull, aching precordial pain, and increasingly severe dyspnea. They performed bilateral costochondral resections and a transverse sternal osteotomy. A year later she had an excellent cosmetic result, was relieved of all symptoms, and had gained 7 pounds in weight. In the discussion of the paper of Ochsner and DeBakey, Sandison reported a 13-year-old girl with a severe pectus excavatum, cyanosis, and dyspnea so severe she was confined to bed. The patient was described as "well and active" after operation.

Brown's (1939)[13] second patient was a 22-year-old man whose exertional dyspnea was relieved by operation. Reporting 7 successful operations, Brown took pectus excavatum out of the group of rare deformities infrequently treated, and established a rational and successful operative procedure which is the basis of most present-day techniques. He resected 2 cm. segments of cartilages 4, 5, 6 and 7 and sectioned cartilage 3, excised the xiphoid process, divided the attachments of rectus and diaphragm to the sternum, performed a transverse wedge osteotomy at the angle of Louis, wired the fifth costal cartilage to the sternum, and used wires for traction on the sternum.

Nissen's (1944)[14] patient, a 20-year-old chemist, complained of shortness of breath, precordial pressure, and easy fatigability. The heart was displaced

*By Dr. Jerome Head.

to the left and rotated so that the right ventricle was in contact with the left chest wall. An electrocardiogram showed an inverted T wave in Lead III and a widened, upward-directed S wave in Leads II and III. In a two-stage operation the sternum was removed, cartilages were resected, and the sternum was turned to lie transversely and with its original ventral surface facing dorsally. No progress reports were given.

Sweet (1944)[15] reported 2 sisters; the 14-year-old girl had attacks of palpitation and tachycardia lasting 4 to 24 hours and associated with pain and cyanosis. The heart was displaced far to the left and enlarged. Sweet's operation, in which the cartilages are wired to the sternum after resection of small chondral segments and a transverse osteotomy of the sternum, improved the appearance of the chest but failed to prevent further paroxysms of tachycardia. The 5-year-old sister of Sweet's first patient had a funnel chest without symptoms.

Lester (1946)[3] reported 8 cases of funnel chest. One patient, a 6-year-old girl, had severe exertional dyspnea and was a patient in the cardiac clinic "for systolic and diastolic murmurs and cardiac incompetence." She was unable to play with other children or to run 50 feet. There was no note on her electrocardiogram. Eighteen months after operation she was completely relieved. A number of the other patients also had definite cardiac symptoms. In older children Lester resected the involved cartilages, separated the xiphoid process, performed a cuneiform osteotomy of the sternum, and used wires for traction on the distal sternal segment.

Teplick and Drake (1946)[16] studied 9 patients, all adults. All had some degree of dyspnea or chest pain attributable to the deformity, none serious. In 8 of the 9 the roentgenograms showed well-marked cardiac displacement to the left. Electrocardiographic changes occurred in almost all: right axis deviation, 2 cases; P wave notching in Leads II and III, 1 case; minor ST elevation in 2 leads, 3 patients. Notching and slurring of the QRS complex was common, especially with an S wave. A definite S wave occurred in 5 patients.

Evans (1946)[17] studied 16 "healthy" subjects with depressed sternum, ranging in age from 15 to 36 years. The apex beat was displaced outward and a systolic murmur was present in every case. In 9 of the cases there was moderate scoliosis.

Sutton's (1947)[18] patient was a 30-year-old woman with severe funnel chest and scoliosis who had increasing dyspnea and palpitation of a few months' duration. She had obvious severe heart failure and dyspnea. The heartbeat was regular at the rate of 140 beats per minute and there was a soft systolic apical murmur. The patient died and autopsy revealed only a dilated heart.

Master and Stone (1949)[19] studied 25 patients with funnel or flat chest referred for consultation because of presumptive diagnosis of heart disease. Sixteen of these patients had funnel chest but the analysis does not distinguish between the 2 groups. In 16 patients the heart was displaced to the left, in 10 the pulmonary artery appeared abnormally prominent, and in 60 per cent a loud systolic murmur was heard. There were varying electrocardiographic changes. Eight patients had precordial pain, 10 had dyspnea, 6 had palpitation, and there was a scattering of other symptoms, such as tachycardia and fatigue.

In a later (1950) report of 42 cases, Lester[20] says that cardiac symptoms produce a decrease in exercise tolerance in nearly all cases and that moderate or incapacitating cardiac disability may occur.

In the discussion of Lester's paper, Brown discussed his experience with 27 cases and stated that he had had uniformly poor end results in symptomatic cases, obtaining only slight improvement in respiratory function although the cosmetic results were good.

Wahren's (1950)[21] patient, a 10-year-old girl, had shown dyspnea and weight loss for a year. The electrocardiogram was normal. Nine months after operation (resection of costal cartilages and xiphoid process, elevation of sternum upon a transversely placed tibial graft) she had gained weight and was free of symptoms.

Dorner and associates (1950)[22] reported a 28-year-old man with a severe pectus excavatum and marked cardiac symptoms. For 18 months he had had palpitation coming on in attacks associated with weakness, dizziness, precordial pain, dyspnea, and sweating. These disabling attacks were induced by slight exercise and relieved by rest. Pulse rate in these attacks was 200 beats per minute. Electrocardiographic studies showed a supraventricular tachycardia with a block varying from 5-1 to 1-1, tall peaked P waves, and a right heart strain pattern. Precordial transition was delayed. Angiocardiographic examination showed dilatation of the right atrium and ventricle. There was a loud systolic murmur in the interventricular intercostal space to the left of the sternum. After operation the symptoms were entirely relieved and the electrocardiogram became normal except for persistence in the delayed precordial transition. The angiocardiograms appeared normal. In the discussion of this case Miscall reported a child with pectus excavatum and severe dyspnea with cardiac displacement. Operation gave complete relief. On this occasion, Brown was more enthusiastic about symptomatic improvement after operation, having abandoned all fixation of the sternum except across the transverse cuneiform osteotomy.

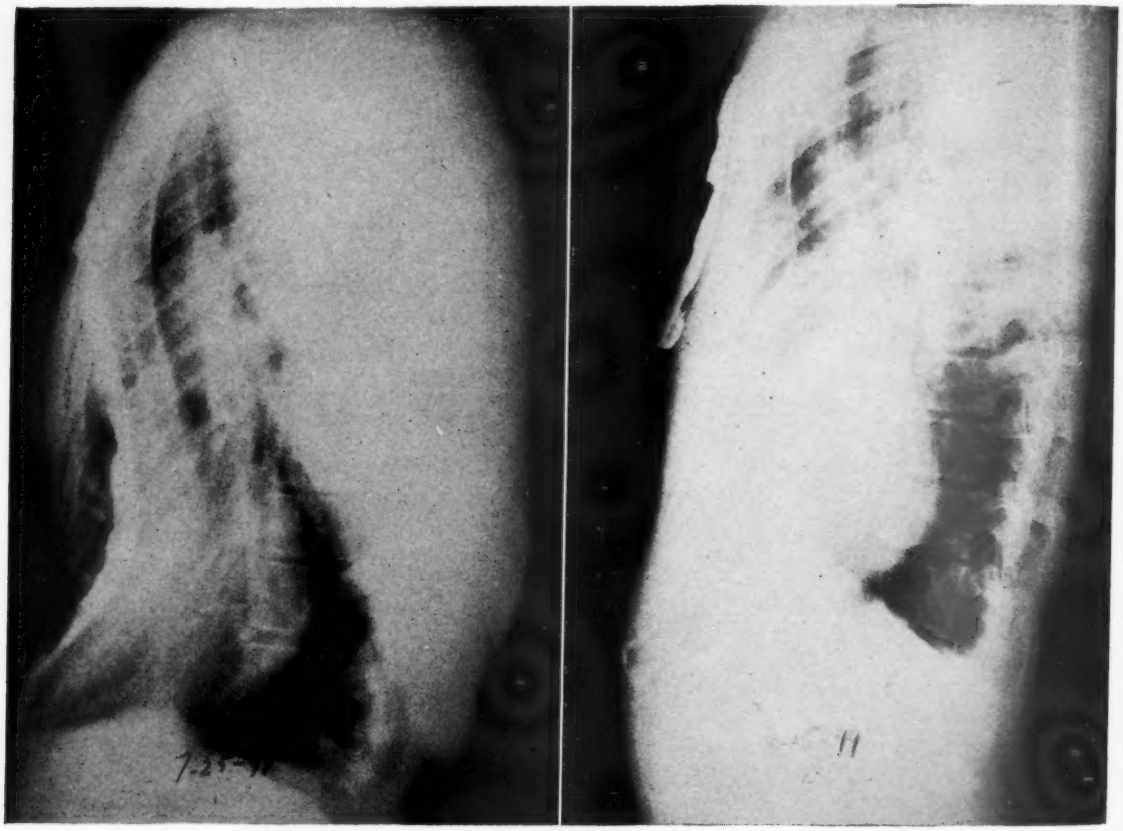
The patient reported herewith had developed auricular fibrillation and cardiac failure. That this may have been due entirely to the deformed chest is strongly suggested by his response to operation and by the results of the physiologic studies performed before and after operation.

W. G. (J. H. H. 503046), a 28-year-old municipal bus driver, was admitted to the hospital June 2, 1949, for a funnel chest deformity causing symptoms. He had had the funnel chest deformity all his life, but said it had become severe during adolescence. There was no history of a similar deformity in the family. He had noticed no disability prior to onset of the present illness and had always been vigorous. Of late he had been aware of a sense of tightness and constraint in the chest. He complained of weakness and fatigability of 1 year's duration, and 2 episodes of heart failure in the 8 months preceding admission. The first episode of failure began 2 or 3 weeks after the onset of pain in the left side of the chest, increasing weakness, and fatigability. He awakened from a sound sleep with severe dyspnea and orthopnea, was hospitalized for 10 days, and then spent 5 weeks at home. He returned to work as a bus driver and remained essentially symptom free for the next 4½ months. Mild exertional dyspnea and a cough with blood-tinged sputum then developed.

Fig. 1 (Patient W. G.).—The patient, a 28-year-old bus driver, had a history of dyspnea, precordial pain, cardiac decompensation, and auricular fibrillation. *A* and *B*, June, 1949, before operation. There is a deep, asymmetrical pectus excavatum. The shoulders are visibly hunched forward. *C* and *D*, October, 1949, 3 months after operation. There is marked improvement in the thoracic contour but less than is possible in very young subjects. The patient no longer had fibrillation, was completely relieved of all cardiac symptoms, and described a sense of freedom and relief from the thoracic constraint which he had felt before.

After 3 weeks of this he had another bout of nocturnal dyspnea and again was hospitalized, with fibrillation and râles at both lung bases. He improved on digitalis and after discharge from the hospital was referred for consideration of surgical correction of the funnel chest. In the 2 weeks since his hospital discharge he had had mild exertional dyspnea.

The patient was a tall (74 inches), gangling, but powerful man with a pronounced funnel chest deformity. The depression extended from nipple to nipple, a distance of 17 cm., with a depth of 7 cm. at the deepest point, the lower end of the sternum. As demonstrated by the photographs (Fig. 1), the entire chest was flattened. The depression began at about the junction of the manubrium and gladiolus and was asymmetrical, curving outward to the left a little below the level of the nipples. There was no paradoxical respiratory movement of the sternum, which appeared fixed. The entire left anterior



A. *B.*

Fig. 2 (Patient W. G.) Lateral roentgenograms. Barium paste applied to the midline outlines the sternal silhouette. *A*, Before operation. The sternum is sharply depressed. The cardiac shadow extends behind the middle of the vertebral bodies, in inspiration. *B*, After operation the sternum is fairly straight, even though a better result might have been achieved if the sternal osteotomy had been performed at a higher level. The posterior border of the cardiac shadow is anterior to the middle of the vertebral bodies, even in expiration.

hemithorax heaved with each heartbeat, and the chest was so flat one could grasp the left side of the chest with one hand from front to back, and obtain the sensation of holding the heart within one's hands under the ribs. The point of maximal impulse was diffuse and far out in the axilla. Rhythm was totally irregular. There was a loud blowing systolic murmur along the left costal border. The liver was palpable just below the costal margin. Results of laboratory studies were as follows: hemoglobin 16.5 Gm.; hematocrit 54 mm.; blood pressure 130/80 mm. Hg; venous pressure 150 mm. water right antecubital vein,

185 mm. left antecubital vein; circulation time (Decholin) arm to tongue 27 seconds on right arm, 35 seconds on left arm; vital capacity 3,100 c.c. Roentgenograms (Fig. 2) showed a deep concavity of the sternum displacing the heart to the left and posteriorly.

The electrocardiogram (Fig. 3, *A*) made June 4, 1949, showed auricular fibrillation. The chest was explored with unipolar leads. Deep S waves were present in V_1 through V_6. In the midaxillary line the R wave was for the first time larger than the S wave and the left ventricular complexes were seen over the posterior chest to the mid-scapular line. The T waves were normal. The apex was markedly displaced so that the left ventricular complexes were not recorded until the electrode reached the midaxillary line and then they extended far around the posterior portion of the left chest wall.

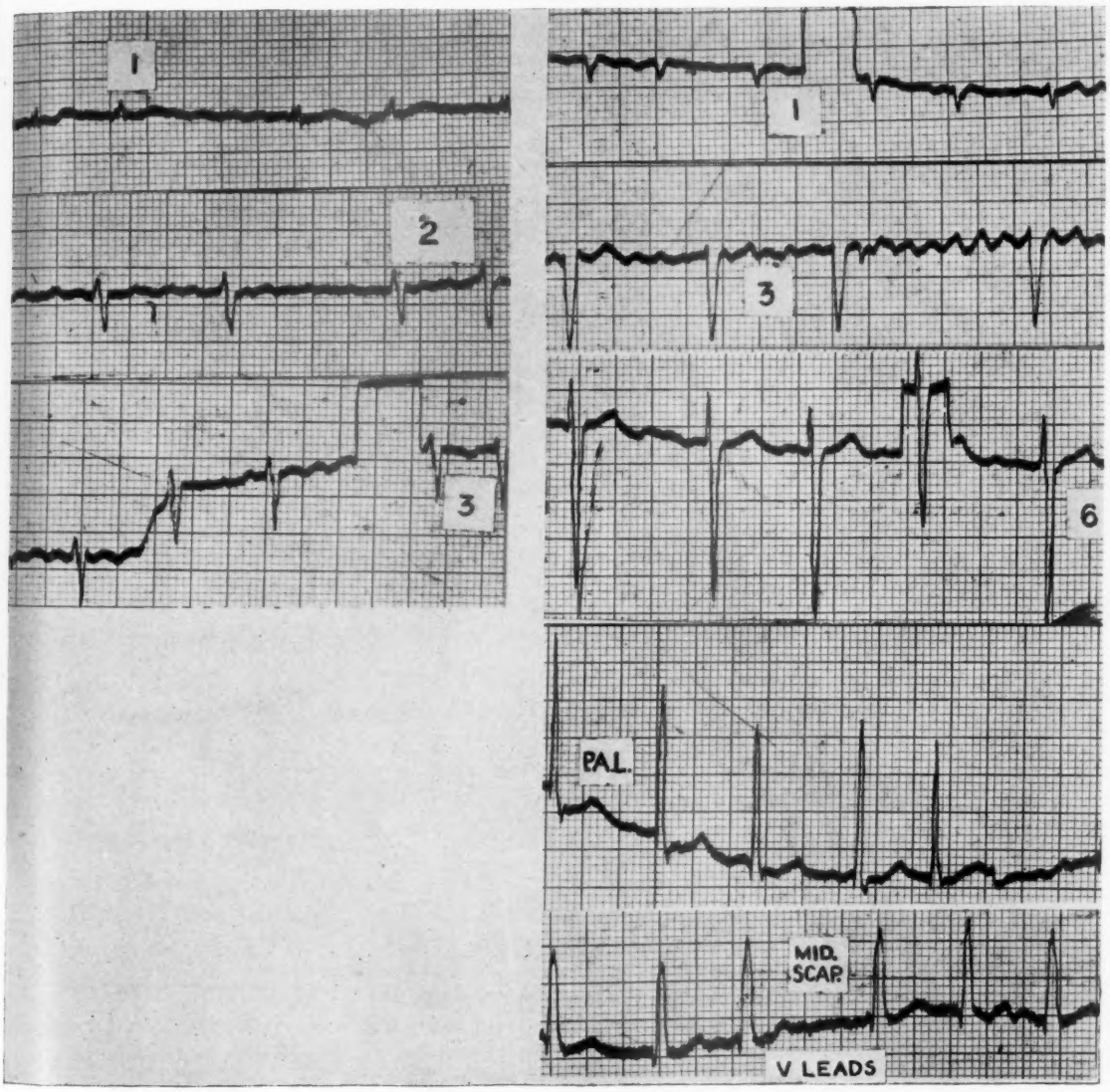


Fig. 3, *A*.—Electrocardiogram, June 4, 1949. Auricular fibrillation. Deep S waves are present in V_1 through V_6. In the midaxillary line the R wave is for the first time larger than the S wave and left ventricular complexes are seen over the posterior chest to the mid-scapular line. The T waves are normal. The apex is markedly displaced so that the left ventricular complexes are not recorded until the electrode reaches the midaxillary line, and then they extend far around the posterior portion of the left chest wall.

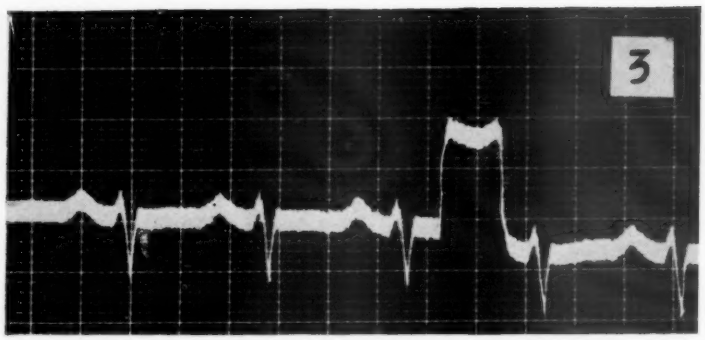


Fig. 3, *B*.—Electrocardiogram, June 13, 1949. After reversion to normal rhythm under quinidine, the patient was still receiving digitoxin and quinidine. Sinoauricular rhythm. Normal R waves, small R_1 in the QRS complexes, T_1 and T_3 isoelectric, T_2 low upright, T_{V_6} normal. Quinidine has restored normal sinus rhythm. The small R_1 is due to the abnormal position of the heart described previously.

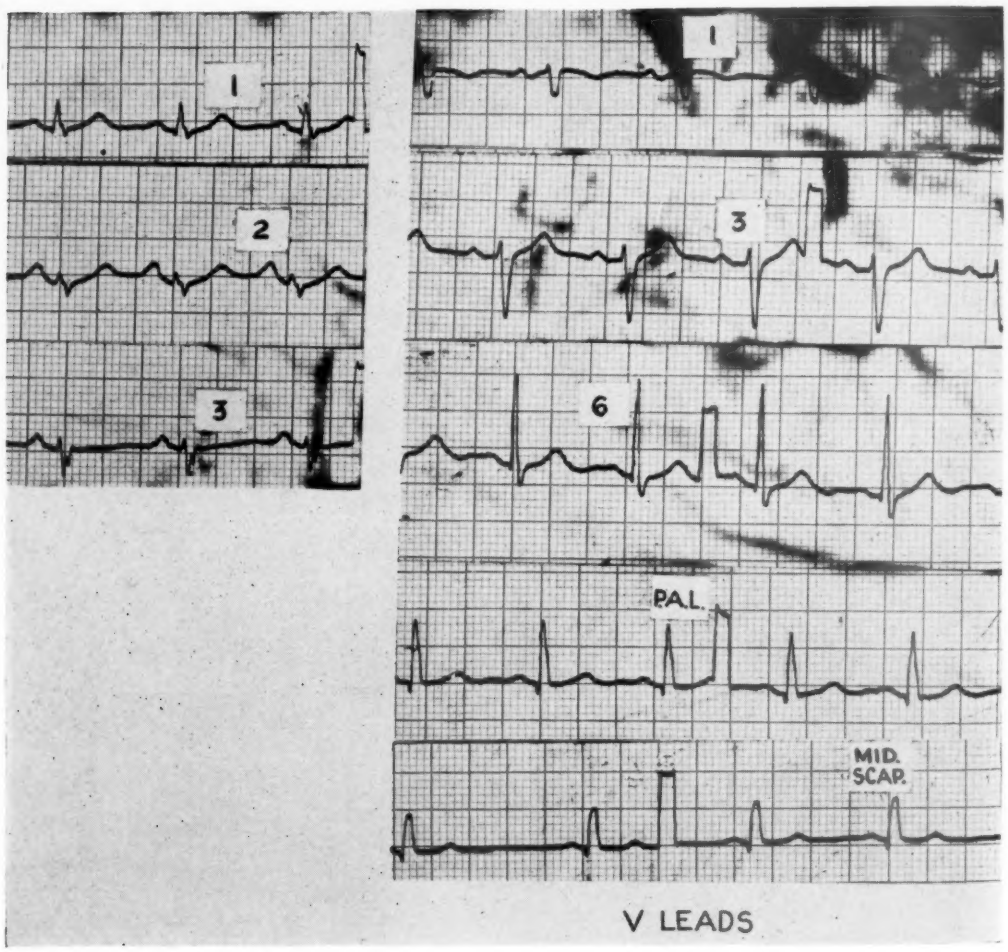
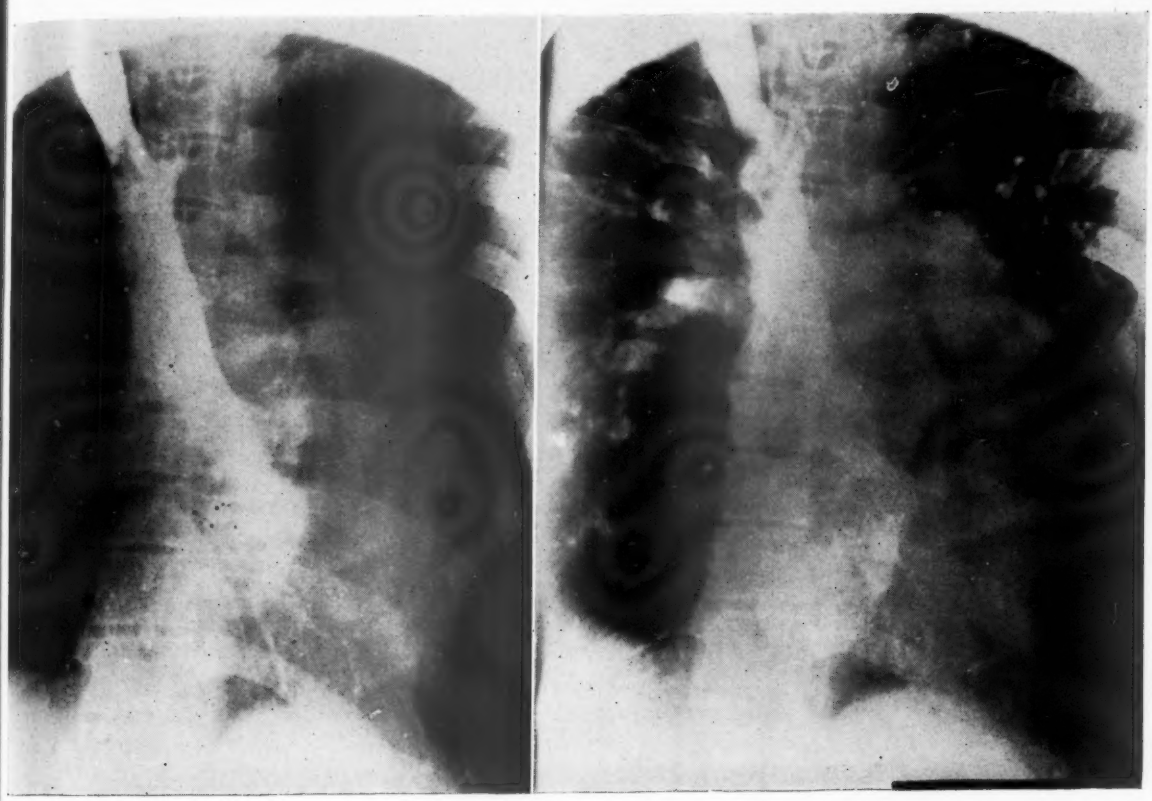


Fig. 3, *C*.—Electrocardiogram, Sept. 18, 1950, 14 months after operation. Rhythm sinoauricular. P wave normal. QRS complexes show slight left axis deviation, normal duration and amplitude with slight delay in precordial transition. There has been little or no change since the electrocardiogram taken in October, 1949, 4 months after operation. Except for slight axis deviation and slight delay in precordial transition the record is within normal limits. Left ventricular complexes are now well developed in V_6, whereas before operation (Fig. 3, *A*) they first appeared in the posterior axillary line.

Cardiac catheterization* (Table I) showed great elevation of right auricular pressure and right ventricular pressure. The cardiac index (the cardiac output per square meter of body surface) was 1.4, about 50 per cent of the expected figure. Respiratory function studies† (Table I) showed a tendency to mild hyperventilation with borderline low figures for ventilatory efficiency.



A. *B.*

Fig. 4 (Patient W. G.).—Angiocardiograms, 1 and 2 seconds after injection of Diodrast. *A*, There is a striking obliquity of the superior vena cava which would ordinarily pass straight down on the right of the vertebral border and parallel to it. The right auricle is well to the left of the vertebrae. *B*, One second later the right ventricle is filled and is seen to lie entirely to the left of the midline. The pulmonary arteries are filling normally. The later views in the series add no information except that the opacity in the right ventricle persists rather longer than usual.

Angiocardiography (Fig. 4) demonstrated marked rotation and displacement of the heart. On quinidine therapy the heart reverted to normal rhythm and the patient was then placed on digitoxin 0.1 Gm. per day and quinidine 0.2 Gm. 3 times a day. The electrocardiogram (Fig. 3, *B*) made on June 13, 1949, showed sinoauricular rhythm, with normal P waves, small R_1 in the QRS complexes, T_1 and T_3 isoelectric, T_2 low upright, and T_{V4} normal. Quinidine restored the normal sinus rhythm. The small R_1 was due to the abnormal position of the heart described previously.

The patient returned for operation, which was performed on July 28, 1949. Segments of 5 costal cartilages on both sides were removed from the sternum medially to the edge of the deformity laterally. As the cartilages on the left were removed the heart moved into the defect and began to press anteriorly until its anterior wall was a good 2 cm. anterior to the

*By Dr. R. J. Bing.
†By Dr. Ross McLean.

TABLE I

	ELECTRO-CARDIOGRAM	CIRCULATION TIME (DECHOLIN) (SECONDS)	VENOUS PRESSURE (MM. WATER)	CARDIAC CATHETERIZATION			RESPIRATORY FUNCTION	
				RIGHT AURICLE (MM. HG.)	RIGHT VENTRICLE (MM. HG.)	CARDIAC INDEX (L./SQ. M./MIN.)	VITAL CAPACITY (L.)	MAXIMUM BREATHING CAPACITY (L./MIN.)
Normal values		14	100	8/0	20/0	3.0	2.8-4.95	82-169
June, 1949	Auricular fibrillation, marked rotation	Right 27 Left 35	Right 150 Left 185	15/8	55/2	1.4	3.51	115
Operation, July 28, 1949								
Oct., 1949	Sinus rhythm, minimal rotation	Right 17 Left 30	Right 105 Left 135	4 (mean)	36/6	2.6	3.4	145
Sept., 1950	Sinus rhythm, minimal rotation	Right 15 Left 18	Right 110 Left 100	6/3	27/2	2.9		

sternal surface. The xiphoid process and sternum were separated, a transverse cuneiform osteotomy was performed at the cephalic end of the sternal deformity, and the sternum lifted anteriorly. As this was done the heart slid medially so that if the sternum had now been released it would have fallen upon the heart. All soft tissue attachments of the corpus sterni were severed. The sternum was fractured at the level of the osteotomy by lifting it forward and was maintained in the corrected position by braided silk sutures in the bone. The pleura was not entered. The heart beat regularly throughout the procedure. The patient did well after the operation except for a marked bradycardia the first afternoon.

The patient was out of bed 48 hours after operation and rapidly became ambulant. Discharge from the hospital was delayed until the twenty-first day because of the necessity for aspirating repeated accumulations of serosanguineous fluid beneath the incision. An electrocardiogram (Fig. 3, *C*) made Aug. 15, 1949, showed that the transition to left ventricular complexes occurred between V_5 and V_6, that is, between the anterior axillary line and the midaxillary line, instead of far posteriorly as before.

The patient returned for re-examination in October, 1949, 3 months after operation. He had taken neither digitalis nor quinidine since discharge and had been asymptomatic. He thought he had a real increase in exercise tolerance and tried to describe a sense of freedom in the chest and a sensation of release from a previous feeling of having the shoulders held forward and inward.

The chest, although still flat and deformed, was greatly improved in appearance. At this time results of laboratory studies were: hemoglobin 16 Gm.; hematocrit 44 mm.; vital capacity 2.81 L.; circulation time, arm to tongue, 17 seconds on right arm, 20 seconds on left arm; venous pressure 100 mm. water right antecubital vein, 130 mm. left antecubital vein. The lateral roentgenogram of the chest showed the heart not to be displaced so far posteriorly as before. Pulmonary function studies now showed perfectly normal figures in all respects. Cardiac rhythm was regular. Cardiac catheterization showed a great drop in the right auricular and right ventricular pressure and an increase in the cardiac index to 2.6, indicating a cardiac output double that before operation.

In September, 1950, 14 months after operation, the patient returned for further studies. He had driven a bus daily, losing no time from work, had taken no medication, and as far as he was concerned had unlimited ability to work and exercise and felt better than he had for years. He now said that he had formerly frequently had a subxiphoid pain which was entirely gone since the operation. There was still a systolic murmur near the apex. Roentgenograms showed no change in the heart unless it had become a little smaller. Venous pressure was now 110 mm. water right antecubital vein and 100 mm. water left antecubital vein. The circulation time with Decholin was 15 seconds on right arm, 18 seconds on left arm. Cardiac catheterization now gave completely normal pressure figures and a cardiac index of 2.9, representing some improvement since October, 1949, although even then the cardiac index had already doubled. The electrocardiogram made on Sept. 18, 1950, showed sinoauricular rhythm and normal P waves. The QRS complexes showed slight left axis deviation, normal duration and amplitude with slight delay in precordial transition. Except for the slight axis deviation and the slight delay in precordial transition the record was within normal limits. There has been no change in the appearance of the patient's record in the past year—that is, since the first return visit after operation.

Comment.—A 28-year-old bus driver had cardiac failure and auricular fibrillation apparently due to a severe pectus excavatum. For a year after operation he has been hard at work, without cardiac symptoms. Heart rhythm is regular, the cardiac output has doubled, and he has had relief from subjective symptoms such as precordial pain and pressure and a sense of thoracic constriction.

Cardiac catheterization has been performed on 3 other patients.

CASE 1.—S. M. (JHH 551059) was a 13-year-old girl who complained of easy fatigability but no real distress. She had a fairly severe funnel chest. An electrocardiogram showed right axis deviation, clockwise rotation, and a slow precordial transition with a deep S in V_6—all evidences of cardiac displacement. Cardiac catheterization demonstrated normal pressures and a normal flow and no abnormalities. She was operated upon Sept. 27, 1950, and a good cosmetic result was achieved. A year later the result remains good. The electrocardiogram has not been repeated.

CASE 2.—P. W. (JHH 542471), an 11-year-old girl, had a striking pectus excavatum without symptoms. Her father had a very severe deformity of this type. Cardiac catheterization showed no abnormalities. On June 29, 1950, the deformity was corrected operatively with a result which has encouraged her father to arrange for a similar operation for himself.

CASE 3.—J. W. (507000), 38-year-old father of Patient P. W., was a rural mail carrier. He had no specific cardiorespiratory symptoms but felt his exercise tolerance was decreasing and that a sense of thoracic constriction was making its appearance. He had an extremely severe pectus excavatum deformity, with the associated secondary postural changes.

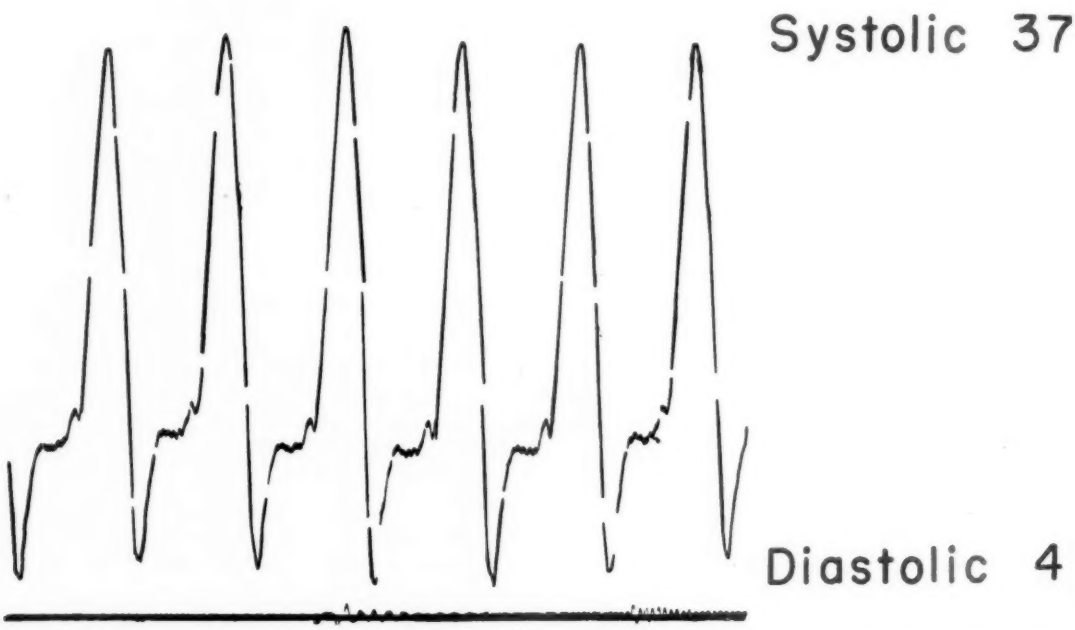


Fig. 5 (Patient J. W.).—Pressure tracing obtained during catheterization of right ventricle of a 38-year-old patient. The plateau which interrupts the normal upswing is interpreted as indicating interference with free movement of the heart in the cardiac cycle.

Cardiac catheterization studies showed normal pressures and a normal cardiac output. However, the pressure tracings (Fig. 5) presented a pattern typical of that seen in constrictive pericarditis. There was a plateau in the right ventricular pressure tracing interrupting the normal upswing. Such a tracing is interpreted as suggestive of interference with free movement of the heart in the cardiac cycle.

DISCUSSION

The mechanism of the production of the cardiac phenomena seen in funnel chest must rest upon the 3 mechanical factors involved—pressure directly upon the heart, displacement of the heart with possible torsion or angulation of the great vessels, and, in the extreme instances, compression of the displaced heart

between the narrowed walls of a distorted hemithorax. The direct pressure may be responsible for the frequency of arrhythmia and the displacement and compression for the mechanical interference with cardiac function. Pulmonary function is apparently less obviously hampered, despite the diminution in the thoracic volume. Measurements of pulmonary function have been disappointing both as indices of disability and as indices of improvement after operation. It would appear that the organism's compensatory mechanisms are so effective as to give normal responses to physiologic investigation of patients with symptomatic distress in a rather wide range until real cardiac embarrassment occurs.

A patient with such severe symptoms as those of J. G., the first patient described, would probably be generally considered as suited for operation. It is true that a striking measure of relief was obtained. However, although his cardiac status now appears to be normal, the patient remains a man with a deformed, flat, thin chest and miserable posture.

We have indicated by the cases cited from the literature that evidences of some effect upon the heart by pressure of the displaced sternum are common, and that appreciable and severe cardiac disability has been reported more often than is generally realized. Nevertheless, the incidence of such difficulties is probably not high enough in itself to warrant a prophylactic operation in childhood or in infancy on that basis alone.

Although in infancy and childhood patients with pectus excavatum rarely appear to have symptoms attributable to it, we feel, for a number of reasons, that operation should be undertaken at as early an age as possible. If the typical flat, thin chest, dorsal kyphos, and forward thrust of the neck are to be prevented or overcome, the earlier the operation, the better the opportunity for such prevention and correction. The sooner the abnormal stresses are removed the better should be the chance for normal growth and development.

In so many instances parents have told us that the children have eaten better and seemed more vigorous after operation that we have come to expect that result as well, obscure as its mechanism may be. Dysphagia has occasionally been reported in the literature in older patients with severe deformity, but we have not observed this symptom thus far. It is true, of course, that the parents tend to be so relieved by the disappearance of the defect and the adoption of better posture and more normal respiratory movements that they may not be entirely objective in their reporting.

The operation in adults is a more laborious and difficult procedure than in children and infants and, while it will correct the depression of the sternum, it will not alter the shape of the shallow thorax nor correct the postural defect. Children and infants tolerate the operation very well and small children are likely to be up and about 2 or 3 days after operation.

For these reasons we have undertaken operation whenever young patients with frank pectus excavatum have presented themselves. In general, the operation is offered to parents as one which will correct the existing defect and will prevent that progression of the defect which would otherwise take place in many cases and give rise to symptoms in some of them.

We have operated upon 19 children ranging in age from 3 months to 12 years and upon 2 adults. The one death, due to massive infection, has been previously reported.[23] In the remaining cases the results have been as satisfactory as the age of the patient would allow, and the younger the patient the better the result. The operative technique is as previously reported.[23] The entire deformed lengths of the involved costal cartilages on both sides—from 3 to 5 cartilages—are resected, the xiphisternal articulation divided, and the body of the sternum freed from all of its connections except to the manubrium. At the cephalic end of the defect a transverse cuneiform osteotomy is performed, the sternum fractured anteriorly, and heavy silk sutures placed across the osteotomy to maintain the correction of the sternal position. No external traction is employed. The corrected position of the sternum is satisfactorily maintained. The operation is well tolerated even by small infants. Paradoxical respiration has not been a problem and no casts or external splints or supports are used. In some children there remains a soft area, just caudal to the sternum, in which paradoxical motion persists for several weeks. The sternum becomes quite rigid after a few weeks and the space on either side gradually becomes solid in most instances.

SUMMARY

Pectus excavatum through displacement and compression of the heart often causes minor cardiac symptoms to appear in adolescence or young adult life with lesser degrees of exercise intolerance. In occasional patients severe cardiac distress occurs. Reported cases of pectus excavatum show an incidence of detectable cardiac abnormality higher than is generally realized.

The case is reported of a 28-year-old man with a severe pectus excavatum and a history of 2 attacks of cardiac failure in 8 months. Electrocardiographic studies showed auricular fibrillation and marked delay in precordial transition indicating cardiac rotation. Cardiac displacement and rotation were shown in the angiocardiogram. Cardiac catheterization showed a cardiac output one-half as great as the expected normal and elevations in the right auricular and ventricular pressures. Circulation time was delayed. Respiratory function studies showed figures at the lower end of the normal range. At operation 5 costal cartilages were resected on either side and a transverse osteotomy of the sternum performed permitting it to be elevated into the corrected position.

A year later the electrocardiogram was normal but for a slight delay in precordial transition, the circulation time was normal, cardiac catheterization showed a doubling of cardiac output to a normal figure and significant fall in the right auricular and ventricular pressures, and respiratory functions were entirely normal. The patient is asymptomatic and has done heavy work the entire year.

Cardiac catheterization in 2 young girls with pectus excavatum which was largely asymptomatic gave essentially normal results. The father of one had a severe funnel chest and in him cardiac catheterization demonstrated a record strongly suggestive of that seen in constrictive pericarditis. In patients with pectus excavatum who show cardiorespiratory symptoms operation should be

undertaken with full expectation of providing relief. However, the operation for this deformity produces its best cosmetic and orthopedic results in the youngest patients and it should be undertaken in infancy or childhood, before the secondary orthopedic deformities are marked or fixed and before cardio-respiratory symptoms have had an opportunity to develop.

REFERENCES

1. Sainsbury, H. S. K.: Congenital Funnel Chest, Lancet **2**: 615-616, 1947.
2. Brown, A. L.: Pectus Excavatum, J. Thoracic Surg. **9**: 164, 1939.
3. Lester, C. W.: The Surgical Treatment of Funnel Chest, Ann. Surg. **123**: 1003-1022, 1946.
4. Sweet, R. H.: Pectus Excavatum, Ann. Surg. **119**: 922-934, 1944.
5. Flesch, M.: Ueber eine Seltene Missbildung des Thorax, Virchow's Arch. f. path. Anat. **57**: 289-294, 1873.
6. Sauerbruch, E. F.: Die Chirurgie der Brustorgane, ed. 3, Berlin, 1928, G. Springer, pp. 735-741.
7. Sauerbruch, E. F.: Operative Beseitigung der Angeborenen Trichterbrust, Deutsche Ztschr. f. Chir. **234**: 760-764, 1931.
8. Hoffmeister, W.: Operation der Angeborene Trichterbrust, Beitr. z. klin. Chir. **141**: 214-227, 1927.
9. Alexander, J.: Traumatic Pectus Excavatum, Ann. Surg. **93**: 489-500, 1931.
10. Carr, James G.: The Cardiac Complications of Trichterbrust, Ann. Int. Med. **6**: 885-894, 1932-1933.
11. Edeiken, J., and Wolferth, C. C.: The Heart in Funnel Chest, Am. J. M. Sc. **184**: 445, 1932.
12. Ochsner, A., and DeBakey, M.: Chōnē-Chondrosternon, J. Thoracic Surg. **8**: 469-511, 1938.
13. Brown, A. L.: Pectus Excavatum, J. Thoracic Surg. **9**: 164-184, 1939.
14. Nissen, R.: Osteoplastic Procedure for Correction of Funnel Chest, Am. J. Surg. **64**: 169-174, 1944.
15. Sweet, R. H.: Pectus Excavatum, Ann. Surg. **119**: 922, 1944.
16. Teplick, J. G., and Drake, E. H.: Roentgen and Cardiac Manifestations of Funnel Chest, Am. J. Roentgenol. **56**: 721-735, 1946.
17. Evans, W.: The Heart in Sternal Depression, Brit. Heart J. **8**: 162-170, 1945-46.
18. Sutton, G. E. F.: Cardiac Anomalies Associated With Funnel Chest, Bristol Med. Chir. J. **64**: 45-48, 1947.
19. Master, A. M., and Stone, J.: The Heart in Funnel Shaped and Flat Chests, Am. J. M. Sc. **217**: 392-400, 1949.
20. Lester, C. W.: Funnel Chest and Allied Deformities of the Thoracic Cage, J. Thoracic Surg. **19**: 507-518, 1950.
21. Wahren, Herman: The Use of a Tibial Graft as a Retrosternal Support in Funnel Chest Surgery, Acta chir. Scandinav. **99**: 568-571, 1950.
22. Dorner, R. A., Keil, P. G., and Schissel, D. J.: Pectus Excavatum, J. Thoracic Surg. **20**: 444-453, 1950.
23. Ravitch, Mark M.: Operative Treatment of Pectus Excavatum, Ann. Surg. **129**: 429-444, 1949.

DISCUSSION

DR. MICHAEL E. DEBAKEY.—I think Dr. Ravitch is to be commended for the observations which have been made in these patients, particularly with regard to the effects on cardiac function. In the earlier observations on these patients it has been well recognized that there was definite clinical evidence of cardiac deficiency and that certainly in the forms of pectus excavatum that are of such a severe nature as are indicated by the case shown in his slide there is almost invariably some evidence of cardiac deficiency. In the milder forms that may be less true. The one thing that would concern me with regard to the long-term effects, however, in this type of operation, would be whether the relief will be maintained. Our experience with this problem, that is, the operative correction of it, is that while even a year after operation there is apparent improvement and maintenance of relief in symptoms as well as relief of deformity, over a long-term period there is an increasing tendency for the deformity to return even though the whole sternum has been removed. Accordingly, I would be a little concerned about the long-term results of any operation which would not in some way fix the mobilized sternum. Fixation by some more substantial method than sutures, even

wire sutures, may be necessary. Even prolonged traction on the mobilized sternum postoperatively has not in our experience prevented the tendency of the deformity to return, and with that return in deformity there is some return in cardiac manifestations of deficiency.

DR. HERBERT C. MAIER.—Cardiac catheterization has been done in two of the adults that I have operated upon for pectus excavatum. Both had a normal cardiac output at rest. On exercise the patient that had the most severe disability showed a marked increase in the right auricular pressure, indicating that there was some difficulty in the blood getting from the right auricle into the right ventricle. There was also an abnormal pressure at rest in the outflow tract of the right ventricle. Unfortunately, we do not have cardiac output measurements on this patient during exercise, but I believe from the other findings that I have mentioned that there would not have been a normal response of cardiac output to exercise. Therefore I wonder whether the cardiac output in some of the other cases, in which it was normal at rest, would increase normally on exercise. Many of these patients have a considerable tachycardia on even slight activity. Cardiac catheterization has been one of the first procedures to give us some clue about the circulatory derangements associated with pectus excavatum.

DR. MARK M. RAVITCH (Closing).—I am sure that the conviction that the cardiac output would have fallen quite markedly during exercise is accurate. The catheterization in our patient was done after he had reverted to a normal rhythm and was not then obviously in heart failure nor did he have fibrillation, although he did have some prolongation in the circulation time. Dr. DeBakey's observation is one which has, of course, worried everybody who has been interested in this problem. We can only say that in children, at least over a period of 5 or 6 years, there has been no tendency for the deformity to recur, and, in spite of the idea that perhaps one would prevent the recurrence of the deformity by strong fixation of the sternum, there is evidence that it is just the other way around. Lincoln Brown pointed out, I think at the last meeting of the American Association for Thoracic Surgery, that, whereas in his early experiences when he was suturing 1 or 2 costal cartilages back to the sternum he got cosmetic relief and no symptomatic relief, since he had abandoned all that fixation he had gotten symptomatic relief in his patients. This is apparently his experience in that regard and must go back only 1 or 2 years. I do not know what his long-term follow-ups are.

THE NATURE OF THE TOXIC MATERIAL IN CLOSED LOOP INTESTINAL OBSTRUCTION; IDENTIFICATION OF LYSOZYME

RUDOLPH A. LIGHT, M.D., NASHVILLE, TENN.

(From the Research Laboratory, Department of Surgery, Vanderbilt University Medical School)

PART I. OBSTRUCTED LOOP CONTENTS

INTRODUCTION

FOR forty years investigators have used the closed loop in experimental intestinal obstruction.[1-6, 45] This method gains the advantages of obviating changes in body electrolytes due to vomiting and, to some extent, those due to poor nutrition. Many observations have been made on the effect of the injection of the contents of the closed loop, prepared in various ways, into normal animals.[3, 4, 7-9] In 1923, Brooks,[10] and in 1934, Brooks and Kirtley,[11] by alcoholic precipitation of loop contents, obtained a powder which, when injected intravenously in very small amounts, was lethal to normal dogs and produced the typical pathologic changes seen after injection of the whole loop contents. The study reported here was made in an attempt to identify this powder, which was thought to have been a ptomaine.

METHODS

One hundred adult mongrel dogs weighing between 5.9 and 20 kg. were used. Without any special preparation beyond the withholding of food for 12 hours intestinal obstruction was produced in 55 animals under sodium pentobarbital anesthesia. A small right rectus incision was used. The ileum was divided 12 inches above the cecum between rubber-shod Allis clamps. Approximately 3 feet above this a second transection of the gut was made. The 2 ends of the loop thus isolated, but with intact blood supply, were inverted with a purse-string suture of 0000 silk and reinforced with 2 to 3 interrupted Lembert sutures of the same material. The continuity of the intestinal tract was reestablished by end-to-end anastomosis utilizing a single layer of through-and through inverting interrupted mattress sutures of 0000 silk. The abdominal wound was closed in layers with silk. Each animal received 100 to 300 c.c. of normal saline beneath the skin, but no other special postoperative care was given.

Various chemical determinations were made at intervals on 16 animals until their deaths. Material from the loops was obtained in 14 animals shortly after death. Material from the loops was obtained in 14 animals shortly after they appeared moribund. Since large quantities of loop material were desired, every dog dying in less than 9 days after operation from any cause, or which had a perforated loop prior to autopsy, was discarded from this series.

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Twenty-eight normal dogs were injected intravenously with material obtained from the obstructed loops: 18 were injected with the whole material, 5 with material which was obtained after high speed centrifugation and passage through a size 02 porcelain filter and found to be sterile, and the remaining 5 with a precipitate obtained as is described in Part II. Blood chemistry determinations in 5 dogs which died from injection of whole material were made at varying intervals from 1 to 5 hours after injection. All blood samples were drawn from the jugular or femoral vein.

RESULTS

In the accompanying tables (Tables I to VI) are shown the weight, hematocrit, serum protein, CO_2 combining power, nonprotein nitrogen, and serum chloride determinations on 5 of 16 dogs. The determinations were obtained at intervals from the time of obstruction until death. Similar determinations on the remaining 11 dogs were discarded because the animals did not live at least 9 days.

TABLE I. PROGRESSIVE WEIGHT CHANGES IN OBSTRUCTED DOGS

Weight (in kilograms)

Postoperative Day	0	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 178	9.7	9.7								9.	8.9		8.7	8.9	8.8	8.7	8.7	8.7		8.5	8.5	8.5					8.5	8.5	8.2
Dog 154	7.8		7.9	7.5	7.3	6.9	6.9	6.7		6.2	6.5	6.3	6.1	6.1	6.		5.4		4.7	4.1	4.1			4.5	4.2	4.			
Dog 174	8.2		7.6	7.9	7.7	7.5	7.4	7.5		7.9	7.7	6.8	6.6	7.			7.	7.1	7.2										
Dog 504	15.8	15.9	15.5	15.3		15.			14.1																				
Dog 44	8.7		8.	8.	7.8		7.9	7.9	7.5	7.2																			

Table I shows the progressive weight loss in 7 dogs. This varied from 1 kg. to a maximum of 3.8 kg. and almost certainly resulted largely from diminished food absorption due to the long length of the isolated bowel.

TABLE II. POSTOPERATIVE HEMATOCRIT VALUES IN OBSTRUCTED DOGS

Hematocrit

Postoperative Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 178	47.5	47.	47.		49.	44.		45.	45.	40.		40.	40.	40.	40.	43.	42.		43.	40.	38.	34.				34.	42.	31.
Dog 44		47.	43.	45.		45.	44.	40.																				
Dog 154		43.	43.	42.	43.		39.		38.	33.	35.	34.	28.					27.	28.									
Dog 174		51.	47.	50.	46.	43.			35.		31.	34.	30.			33.		29.										
Dog 81	48.			60.		42.	44.	39.			38.	37.	38.															

In Table II, it is seen that in every case there was a progressive fall in the hematocrit varying from a minimum of 1.5 to a maximum of 22. Except for Dog 174, which died on the twentieth day with a fall of 22, and Dog 178, which died on the twenty-ninth day with a fall of 16.5, this decline was proportional to the length of time of survival. Although in some cases there was hemoconcentration in the immediate postoperative period, this progressive anemia is in accord with the findings of Martin and associates[12] in large resections of small bowel in human beings.

However, Table III reveals that there was no significant change in serial plasma protein determinations and, although not shown, there were no significant changes in the albumin-globulin ratios which were determined in 4 cases. This discrepancy is explained by the fact that hemolysis appeared in the serum

TABLE III. TOTAL SERUM PROTEINS (GM. PER 100 C.C.) VALUES IN OBSTRUCTED DOGS

Proteins

Postoperative Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 178	5.77	5.98	6.07		6.05	5.89		5.84	5.66	5.83		5.66	5.78	5.71	6.34	5.32	5.82		5.49	5.68	5.67	5.66				5.83	5.77	5.17
Dog 44		7.70	6.55	7.44			7.27	6.68																				
Dog 154		5.70	6.25	6.42	5.86		5.35		6.27	5.07	5.12	5.48	5.83					6.13	5.65									
Dog 174			7.00	6.35	6.54	6.37			6.11		5.43	6.30	6.02			6.20		5.69										
Dog 81	5.32			6.60		6.22	5.60	4.93			5.70	5.69	5.98															

despite the most careful technique, including drawing the specimens under oil. Apparently intravascular hemolysis occurred, although no previous report of this phenomenon has been found. Unfortunately, urinalyses were not made, but quite possibly hemoglobinuria was present.

TABLE IV. CARBON DIOXIDE COMBINING POWER (VOLUMES PER 100 C.C.) VALUES IN OBSTRUCTED DOGS

CO_2

Postoperative Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 176	44.9	43.6	35.6		44.9	45.8		48.	50.	38.4		37.4	53.2	44.9	46.7	50.4	42.1		36.5	36.5	40.3	41.2				41.2	36.3	34.7
Dog 44		42.8	62.5	58.8		57.9	61.6	56.																				
Dog 154		33.8	37.4	39.3	33.8		43.		43.	Q.N.S.	40.3	41.2	36.5					38.4	41.2									
Dog 174		43.8	43.9	39.3	50.4	34.7			43.9		41.2	40.3	45.8			41.2		39.3										
Dog 81	31.9			49.1		48.6	44.9	37.4			44.9	43.9	45.8															

TABLE V. NONPROTEIN NITROGEN (MG. PER 100 C.C.) VALUES IN OBSTRUCTED DOGS

N. P. N.

Postoperative Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 178	33	31	28		33	30		34	29	32		30	40	37	36	26	33		29	40	29	32				32	42	51
Dog 154		24	36	26	27		26		34	24	30	30	27					27	25									
Dog 115		28		30	30	30	26	30																				
Dog 174		31	30	34	32	30			33		30	27	28			29		40										
Dog 81	26			38		26	23	30			23	25	24															

TABLE VI. SERUM CHLORIDES (MEQ. PER LITER) VALUES IN OBSTRUCTED DOGS

Serum Chloride

Postoperative Day	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Dog 178	109.2	108.	111.3		112.5	114.5		110.4	113.7	110.1		117.9	113.4	115.5	106.5	100.1	110.4		113.4	109.8	116.1	108.6				102.	97.	92.7
Dog 154		101.1	98.1	99.9	104.7		97.5		97.8	92.4	99.6	96.6	100.2					93.3	95.1									
Dog 174		93.	91.8	98.1	99.3	108.6			107.7		108.	111.9	Q.N.S.			105.0		114.6										
Dog 81	111.1			94.5		100.5	101.2	104.6			102.6	109.8	104.1															
Dog 504	103.8	102.9	102.9		105.			104.7																				

Although Tables IV, V, and VI show some variations, there were no significant serial changes in CO_2 combining power, nonprotein nitrogen, or serum chlorides, and certainly no marked change in pH is indicated by the latter.

Tissue and serum potassiums were done in 5 dogs at intervals from the second postoperative day until death. Tissue values varying from 130 to 142

meq. per liter and serum values of 4 to 6 meq. per liter were found. Although the effects of intravascular hemolysis must be considered, these are within the normal ranges and are in agreement with the results of Schilling and associates[3] and Bellet and colleagues,[13] who concluded that potassium abnormalities play no part in the toxemia of experimental or human intestinal obstruction.

TABLE VII. BLOOD CHEMISTRY DETERMINATIONS AFTER INTRAVENOUS INJECTION OF WHOLE OBSTRUCTED LOOP CONTENTS INTO 5 NORMAL DOGS

DOG NUMBER	HOURS AFTER INJECTION	N P N (MG. %)	PROTEINS (GM. %)	CO_2 (VOL. %)	HEMATOCRIT (% CELLS)	SERUM CHLORIDE (MEQ./L.)
38	2	38	4.84	25.3	51	105.9
	3	40	4.74	25.4	52	107.1
X-Y-Z	1	50	5.82	22.6	43	101.7
	2 hrs. and 50 min.	63	6.72	20.8	45	110.0
117	5 min. prior to injection	30	6.29	36.5	43	117.3
	5	45	5.19	32.8	59	116.4
135	2	29	6.22	25.4	42	112.5
	3	29	6.47	26.3	43	114.6
135A	1	25	5.88	39.3	35	108.6
	3	24	6.60	33.3	34	107.7

Table VII shows the blood determinations at intervals of 1 to 5 hours after intravenous injection of 0.5, 0.9, 0.9, 0.9, and 1.4 c.c. per kilogram body weight of whole toxic material into 5 normal dogs. It will be seen that there are no significant changes in the nonprotein nitrogen, protein, CO_2, or serum chlorides. It is interesting that there is no significant change in the hematocrit. However, reference to Table II reveals that in the obstructed dogs there are no changes in hematocrit prior to the sixth day after obstruction and in most cases this does not occur until at least the ninth day. This may be the result of the beginning of absorption of toxic material from the intestinal tract. These dogs all showed the typical symptom complex and pathologic changes and died in 3 to 6 hours. Apparently death supervened before any changes in hematocrit could become manifest and no significant intravascular hemolysis occurred.

Fig. 1 shows the first 2½ hours of a kymographic record of blood pressure. These were made in 5 animals and shock, as evidenced by fall of blood pressure, except initially and terminally, was not found. Gatch and associates[14] used this transitory fall in blood pressure as a measure of toxicity of injected materials. This finding was constant and was nearly always accompanied by an equally transient increase in rate and depth of respiration in our experiments and we believe that this is a pulmonary phenomenon.

The pattern of events was the same in all 5 experiments. One record which is typical of all in this series, as well as those reported by other investigators,[4, 6, 13, 15, 16] is presented.

Dog 117, a Collie type female, weight 13.3 kg., was studied on April 18, 1950.

11:15 A.M. With the animal under Nembutal anesthesia, the right femoral artery was cannulated and connected to a recording manometer.

11:30 A.M. Blood was drawn for chemical analysis.

11:35 A.M. After normal blood pressure record was made, 6 c.c. of loop material from Dog

517 were injected into the femoral vein. There was an immediate fall in blood pressure with return to normal in 15 minutes, and an increase in depth and rate of respirations during this period.

11:38 A.M. The dog had a large normal bowel movement.

11:40 A.M. The dog urinated.

1:00 P.M. Blood pressure at 15 minute intervals showed no fall.

3:00 P.M. There was excretion of liquid stools with some blood. Anuscopic examination showed intense reddening of lower rectum.

4:30 P.M. Blood was drawn for chemical analysis. The animal made retching movements of the abdomen. There was no vomiting (probably due to anesthesia).

4:45 P.M. Blood pressure was falling, and there were retching abdominal movements.

4:50 P.M. Respirations ceased after having been increased in rate for 30 minutes. The heart stopped shortly thereafter.

Autopsy.—The entire intestinal tract was removed in toto. (No other organs were examined in this case as repeated examinations have shown no other significant abnormalities.[1, 3, 4, 17]) The stomach was normal in appearance. There was a sharp line of demarcation just below the pylorus with reddened, thickened duodenal mucosa, and reddened jejunum with scattered small petechial hemorrhages. There was a gradual change to normal bowel at the terminal ileum. The entire colon was dusky. (See Fig. 2.) Microscopic sections showed marked engorgement of the submucosal vessels and scattered areas of hemorrhage.

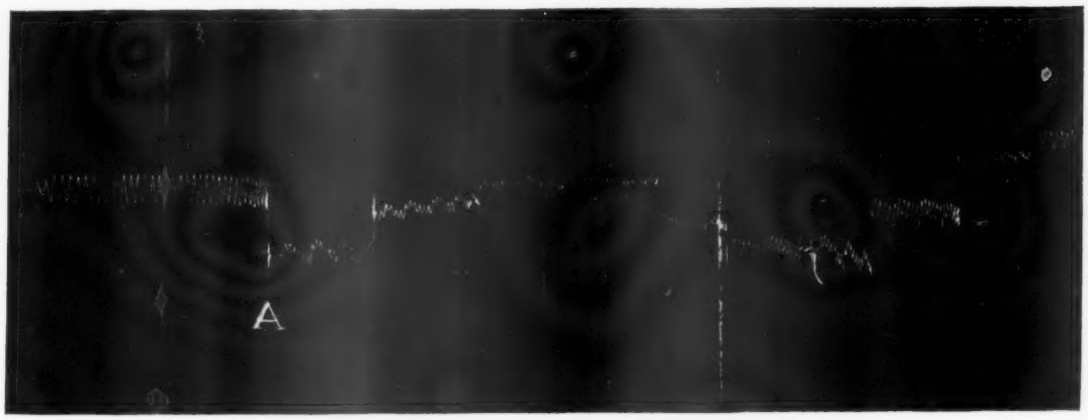

Fig. 1.—Kymograph record of femoral artery blood pressure after intravenous injection of whole obstructed loop contents into a normal dog at *A*. Each plateau represents a 15 minute interval.

DISCUSSION

The preceding findings rule out any marked chemical changes as the cause of death in closed loop obstruction and also in injected animals. This is in agreement with Pearse,[6] who found no significant changes in nonprotein nitrogen, chlorides, or CO_2, but did find a progressive anemia, and Cooper,[18] whose excellent review states that no significant chemical changes were found by other workers. As has been noted, shock, as evidenced by diminished blood pressure, apparently plays no part in death of the animal following intravenous injection of loop contents. Heuer and Andrus[19] considered that the initial fall in blood pressure is evidence of primary shock and is due to vasodilatation, and quote the work of Pearce and Eisenbrey[20] as proof of this. However, recent work by Gross and Brown[21] indicated that anaphylactic phenomena may have their origin from blockage of the pulmonary circulation and the clinical response of these animals would seem to confirm this. Heuer and Andrus found that the

injection of adrenal cortical extract had a protective action against what they termed "secondary shock." However, this investigation did not reveal the secondary shock which they described except as a terminal event. This is in agreement with Nemir and associates[37] and, therefore, it is felt that this phenomenon is ruled out as a primary cause of death.

Sarnoff and Poth,[26] Lockwood and associates,[23] Sarnoff and Fine,[25] Blain and co-workers,[27, 28] and others[24, 29, 30] have shown the protective action of antibiotic and chemotherapeutic agents in obstructed and strangulated intestines. Harper and Lemmer[31] and Poth and McClure[22] showed experimental evidence that bacteria play an important part in damaging the intestinal mucosa so that absorption through it may take place. Laufman and associates[32] showed conclusively that sterilized, devascularized intestine within the peritoneal cavity undergoes autolysis with no adverse effects. The work of these authors is in agreement with the assumption of Murphy and Brooks[3] and others that the origin of the toxin in intestinal obstruction is bacterial.

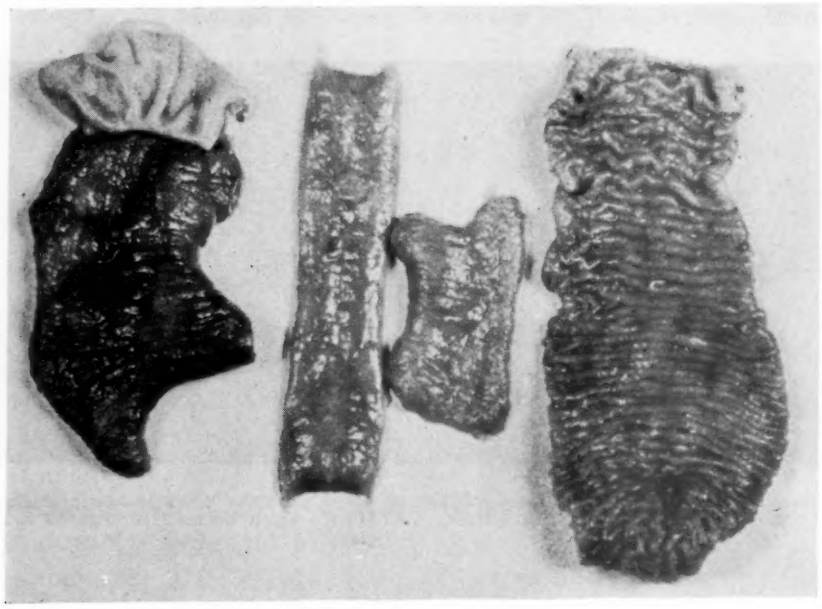

Fig. 2.—From left to right, portions of: stomach and duodenum, upper jejunum, terminal ileum, and midcolon of an animal dying from intravenous injection of whole obstructed loop contents.

CONCLUSIONS

Changes in body chemistry and shock are not the cause of death following the intravenous injection of closed loop contents.

Part II. Lysozyme

INTRODUCTION

The effect of intra-arterially administered lysozyme on the gastrointestinal mucosa is described by Prudden, Meyer, and co-workers.[33] In patients with chronic nonspecific ulcerative colitis they found a great increase of fecal lyso-

zyme content during an exacerabtion and a fall during a remission of the disease.[34] They and Wang and colleagues[35, 36] also have produced gastric ulcers by the administration of lysozyme by mouth. Furthermore, they injected 360,000 units into the superior mesenteric artery[33] and produced almost exactly the gross and microscopic intestinal lesions described in Part I of this paper and by other investigators.[1, 3, 4, 37]

Lysozyme is a small molecule protein with a molecular weight of about 17,500. It contains 15 per cent N, sulfur as sulfhydryl, and a small amount of phosphorus.[38] It was identified by Fleming in 1930[39] in human tears, nasal secretions, and egg white, and subsequently in other tissues. It can be crystallized from egg white into thin rectangular plates.[40] It is soluble in acid but not in organic solvents and is precipitated by ether, acetone, and alcohol. A unit equals the smallest amount which will cause complete lysis of the *Micrococcus lysodeikticus* in a serial dilution test.

METHODS

The lysozyme activity of obstructed loop contents was determined in 8 animals. Injection of the loop contents from these animals was made into 8 normal dogs.

Lysozyme activity of the small bowel content of 3 normal dogs was determined prior to obstructing them.

Pure lysozyme crystals,* dissolved in normal saline solution and acidified with 0.1 N HCl, were then injected intravenously into 17 normal dogs in amounts varying from .0015 mg. per kilogram to .29 mg. per kilogram (20 to 5,000 units). Lysozyme is difficult to dissolve and in many cases the solution was cloudy or showed evidence of particulate matter. However, the solution was stirred vigorously and it was felt that a fair sample was obtained.

Samples of obstructed loop contents from 5 dogs were centrifuged at 3,000 r.p.m. for one hour and the supernatant fluid poured off. The centrifugate, which had the appearance of gross fecal particles, was called Fraction 1. The supernatant fluid was then precipitated with an equal volume of absolute alcohol, centrifuged, and the precipitate called Fraction 2. Reprecipitation of the supernatant fluid with an equal volume of alcohol and centrifugation resulted in Fraction 3. The same process was repeated to obtain Fraction 4. Further addition of alcohol gave no further precipitation and the fluid was clear and had the odor of pure alcohol. The 4 fractions thus obtained from each sample were dried in air and assayed for lysozyme activity. This was done by measuring the rate of change in viscosity of the mucopolysaccharide obtained from the *M. lysodeikticus* in an Ostwald viscosimeter.

Twenty milligrams of Fraction 3 from each of the 5 dogs were re-dissolved and injected intravenously into 5 normal animals.

RESULTS

No lysozyme activity was found in the jejunal and ileal contents of normal dogs.

*Purchased from Nutritional Biochemical Corporation.

Lysozyme activity of the loop material obtained from 8 dogs was found to vary from 2 units to 20 units per cubic centimeter. This enzyme is inactivated by oxidation and the determinations of toxic material in duplicate can be correlated only if done immediately. As a consequence it was felt that the minimum activity was determined.

On intravenous injection of the above loop contents into 8 normal dogs, it was found that if the fluid contained less than 5 units per cubic centimeter the animal did not die, but a typical symptom complex ensued. There was almost immediate urination and/or defecation, nausea, vomiting, and evidence of illness for a period of several hours. If the fluid contained more than 5 units per cubic centimeter, the animal invariably died in 19 hours or less (3 to 19 hours), with the preceding typical symptoms and ultimate collapse and death. Examination of the intestinal tract revealed changes similar to those obtained from the intravenous injection of whole loop contents.

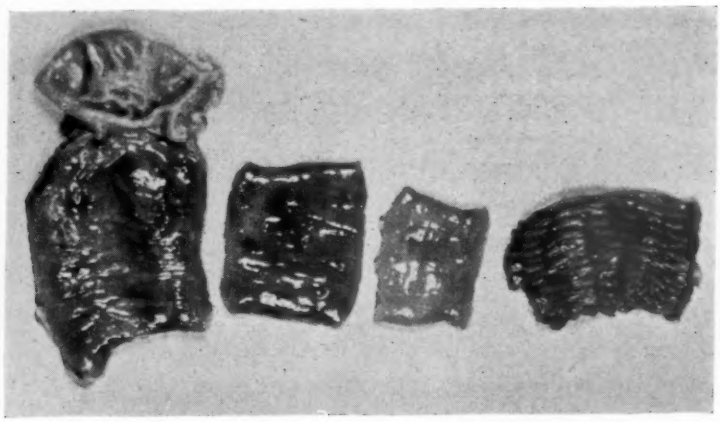

Fig. 3.—From left to right, portions of: stomach and duodenum, upper jejunum, terminal ileum, and midcolon of an animal dying after intravenous injection of 2,000 units of lysozyme.

Of 17 dogs injected with pure lysozyme crystals dissolved in saline solution, 5 dogs died within 3½ to 48 hours. Five were destroyed after 2½ to 9 hours. All showed the same symptom complex and the typical pathologic picture seen after the injection of whole loop contents (Fig. 3). Two dogs showed symptoms of toxicity manifested by urination and/or defecation, nausea, and sometimes vomiting, but they recovered. Five dogs were unaffected. There seemed to be no correlation between the absolute amount administered and the evidences of toxicity. However, dilute solutions apparently had more effect than did concentrated solutions. This is probably explained by the difficulty in dissolving the crystals.

Of the 4 fractions obtained by precipitation and centrifugation, Fraction 1 showed less than 1 unit of lysozyme activity per milligram; Fractions 2 and 3 contained 3 to 6 units per milligram in each; and Fraction 4 again showed only a trace of activity. Injection of 20 mg. of the re-dissolved Fraction 3, which was a light tan powder, produced the typical symptom complex, death, and the typical intestinal changes seen after the injection of pure lysozyme or whole loop contents.

DISCUSSION

Many substances, histamine,[1, 40] nucleoproteins,[41] ptomaines,[4] and others, have in the past been felt to play a part in toxicity if they are not the toxic substances themselves. More recently, Tanturi and co-workers[42, 43] have identified lecithinase and hyaluronidase in experimental intestinal obstruction and feel that these substances are among the products of strangulated intestine which cause death. Cultures were made on the obstructed loop contents of 5 animals and in every case showed Welch organisms; however, intravenous injection of these materials has not been done to determine whether they would produce the same pathologic picture in the intestines. Nemir and collaborators,[15, 37] in strangulated obstructed loops, have identified a characteristic absorption spectrum of peritoneal fluid which is toxic and which, on intraperitoneal injection into a normal animal, produces similar submucosal changes in the gastrointestinal tract. They did not inject their material intravenously and possibly the picture might have been more similar to those of this and other investigators had they done so.

Cole and associates[44] described a picture of intestinal hemorrhage and congestion, most marked in the duodenum and fading in the ileum following the intravascular injection of massive doses of curare, in sufficient amount to cause death. This is accompanied by similar changes in the pancreas, spleen, and lungs. They felt that this was due to shock. Although the present author and other investigators have not found abnormalities in other organs, the intestinal picture described by Cole is markedly similar to that produced by loop contents and lysozyme. Large amounts of lysozyme (500,000 units) injected rapidly into the femoral vein cause immediate collapse and death in 5 minutes with hemorrhages in every organ (the brain was not autopsied) and prevent in vitro clotting of the blood for at least 5 days. However, since we have produced the intestinal picture they described with but transient fall in blood pressure, it seems likely that loop contents and lysozyme differ in action from curare. Brooks and Kirtley,[11] in 1934, gave 19 mg. of a doubly alcohol-precipitated residue to a 6½ kg. dog with death in 2 hours and the same typical intestinal picture. They repeated this many times. In each case it was the second alcohol precipitate which was the most toxic. The present findings, that precipitates 2 and 3 contain the highest titer of lysozyme activity, further implicate lysozyme as one of the toxic elements in closed loop obstruction.

CONCLUSIONS

1. Intravenous injection of the contents of a closed obstructed intestinal loop into normal animals produces a typical clinical and pathologic picture.

2. It was shown in a small series of experiments that this material is not lethal if it contains less than 5 units per cubic centimeter of lysozyme.

3. Intravenous injection of pure lysozyme may produce the same clinical and pathologic changes as does obstructed loop material.

4. No lysozyme activity is found in the normal small bowel content of dogs.

5. It appears that lysozyme is a toxin present in closed loop intestinal obstruction.

6. Investigation of lysozyme content in obstructed human bowel should be made.

The author wishes to express appreciation to Dr. Ann Minot, Associate Professor of Biochemistry and Director of the Clinical Chemical Laboratory, Vanderbilt University Medical School, for help and advice in the biochemical determinations; to Dr. Roy C. Avery, Associate Professor of Bacteriology and Director of Bacteriological and Serological Laboratory, Vanderbilt University Medical School, for supplying cultures of *M. lysodeikticus;* to Dr. David L. McVickar, Assistant Professor of Bacteriology, Vanderbilt University Medical School, for preparation of sterile loop contents; and especially to Dr. Margaret E. Greig, Associate Professor of Pharmacology, Vanderbilt University Medical School, and Dr. William C. Holland, Instructor in Pharmacology, for potassium determinations and lysozyme assays.

REFERENCES

1. Stone, H. B., Bernheim, B. M., and Whipple, G. H.: Intestinal Obstruction: A Study of the Toxic Factors, Bull. Johns Hopkins Hosp. **23:** 159-165, 1912.
2. Copher, G. H., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Therapeutic Value of the Administration of Sodium Chloride, Ann. Surg. **78:** 755-760, 1923.
3. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Causes of Symptoms and Death, Arch. Int. Med. **15:** 392-412, 1915.
4. Brooks, B., Schumacher, H. W., and Wattenberg, J. E.: Intestinal Obstruction: An Experimental Study, Ann. Surg. **67:** 210-214, 1918.
5. Schilling, J. A., McCoord, A. B., and Clausen, S. W.: Potassium Loss in Experimental Intestinal Obstruction, Surg., Gynec. & Obst. **92:** 1-13, 1951.
6. Pearse, H. E.: Experimental Chronic Intestinal Obstruction From Blind Loops, Surg., Gynec. & Obst. **59:** 726-734, 1934.
7. Albeck, V.: Experimentelle und klinische Untersuchungen über die Todesursache bei Dünndarmstrangulation, Arch. f. klin. Chir. **65:** 569-615, 1902.
8. Ellis, J. W.: Cause of Death in High Intestinal Obstruction, Ann. Surg. **75:** 429-448, 1922.
9. Murphy, F. T., and Vincent, B.: An Experimental Study of the Cause of Death in Acute Intestinal Obstruction, Boston M. & S. J. **165:** 684-693, 1911.
10. Brooks, B.: Personal communication.
11. Brooks, B., and Kirtley, J. A.: Personal communication.
12. Martin, J. D., Jr., Robertson, R. L., and Dennis, E. W.: Anemia Following Resection of Intestine, SURGERY **24:** 819-827, 1948.
13. Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M.: Effect of Vomiting Due to Intestinal Obstruction on Serum Potassium: Chemical and Electrocardiographic Observations in Fifteen Cases. Preliminary Report, Am. J. Med. **6:** 681-804, 1949.
14. Gatch, W. D., Trusler, H. M., and Lyons, R. E., Jr.: Toxemia in Acute Intestinal Obstruction: Toxicity of Intestinal Contents, With Special Reference to the Pancreaticoduodenal Secretion, Arch. Surg. **28:** 1102-1120, 1934.
15. Nemir, P., Jr., Hawthorne, H. R., Cohn, I., Jr., and Drabkin, D. L.: The Cause of Death in Strangulation Obstruction: An Experimental Study. I. Clinical Course, Chemical, Bacteriologic and Spectrophotometric Studies, Ann. Surg. **130:** 857-873, 1949.
16. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction. I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16:** 606-614, 1928.
17. Stone, H. B.: The Toxic Agents Developed in the Course of Acute Intestinal Obstruction, and Their Action, Surg., Gynec. & Obst. **32:** 415-419, 1921.
18. Cooper, H. S. F.: The Cause of Death in High Obstruction, Arch. Surg. **17:** 918-967, 1928.
19. Heuer, G. J., and Andrus, W. DeW.: The Effect of Adrenal Cortical Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, Ann. Surg. **100:** 734-749, 1934.
20. Pearce, R. M., and Eisenbrey, A. B.: A Study of Experimental Conditions of Low Blood Pressure of Non-Traumatic Origin, Arch. Int. Med. **6:** 218-230, 1910.
21. Gross, P., and Brown, J. H. V.: The Mechanism of the Anaphylactoid Phenomenon, Am. J. M. Sc. **221:** 46-50, 1951.
22. Poth, E. J., and McClure, J. N., Jr.: Intestinal Obstruction, Ann. Surg. **131:** 159-170, 1950.
23. Lockwood, J. S., Young, A. D., Bouchelle, McL., Bryant, T. R., Jr., and Stojowski, A. J.: Appraisal of Oral Streptomycin as an Intestinal Antiseptic, With Observations on Rapid Development of Resistance of E. Coli to Streptomycin, Ann. Surg. **129:** 14-21, 1949.
24. Laufman, H.: Experimental Evidence of Factors Concerned in the Eventual Recovery of Strangulated Intestine: Effects of Massive Penicillin Therapy, SURGERY **28:** 509-515, 1950.

25. Sarnoff, S. J., and Fine, J.: The Effect of Chemotherapy on the Ileum Subjected to Vascular Injury, Ann. Surg. **121**: 74-82, 1945.
26. Sarnoff, S. J., and Poth, E. J.: Intestinal Obstruction. I. The Protective Action of Succinylsulfathiazole Following Simple Venous Occlusion, SURGERY **16**: 927-931, 1944.
27. Blain, A., III, and Kennedy, J. D.: The Effect of Penicillin in Experimental Intestinal Obstructions. Studies on Strangulated Low Ileal Obstruction, Bull. Johns Hopkins Hosp. **79**: 1-20, 1946.
28. Blain, A., III: Penicillin in Experimental Intestinal Obstruction. A Summary of Observations With Reference to Their Clinical Application, Surg., Gynec. & Obst. **84**: 753-758, 1947.
29. Davis, H. A., Gaster, J., Marsh, R. L., and Pritel, P. A.: The Effect of Streptomycin in Experimental Strangulation of the Bowel, Surg., Gynec. & Obst. **87**: 63-67, 1948.
30. Harper, W. H., and Blain, A., III: The Effect of Penicillin in Experimental Intestinal Obstruction. Preliminary Report on Closed Loop Studies, Bull. Johns Hopkins Hosp. **76**: 221-244, 1945.
31. Harper, W. H., and Lemmer, R. A.: Necrosis and Ulceration of the Intestinal Wall in Simple Intestinal Obstruction, Bull. Johns Hopkins Hosp. **79**: 207-228, 1946.
32. Laufman, H., Martin, W. B., Method, H., Tuell, S. W., and Harding, H.: Observations in Strangulation Obstruction. II. The Fate of Sterile Devascularized Intestine in the Peritoneal Cavity, Arch. Surg. **59**: 550-564, 1949.
33. Prudden, J. F., Lane, N., and Meyer, K.: The Effect of Orally and Intra-arterially Administered Lysozyme on the Canine Gastrointestinal Mucosa, Am. J. M. Sc. **219**: 291-300, 1950.
34. Meyer, K., Gellhorn, A., Prudden, J. F., Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease. II. Lysozyme Activity in Chronic Ulcerative Colitis, Am. J. Med. **5**: 496-502, 1948.
35. Wang, K. J., Grant, R., Janowitz, H. D., and Grossman, M. I.: Action of Lysozyme on Gastrointestinal Mucosa, Arch. Path. **49**: 298-306, 1950.
36. Meyer, K., Prudden, J. F., Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease. I. Lysozyme in Peptic Ulcer, Am. J. Med. **5**: 482-495, 1948.
37. Nemir, P., Jr., Hawthorne, H. R., Cohn, I., Jr., and Drabkin, D. L.: The Cause of Death in Strangulation Obstruction: An Experimental Study. II. Lethal Action of the Peritoneal Fluid, Ann. Surg. **130**: 874-880, 1949.
38. Meyer, K., Thompson, R., Palmer, J. W., and Khorazo, D.: The Purification and Properties of Lysozyme, J. Biol. Chem. **113**: 303-309, 1936.
39. Fleming, A.: On a Remarkable Bacteriolytic Element Found in Tissues and Secretions, Proc. Roy. Soc., London, s. B. **93**: 306-317, 1922.
40. Alderton, G., Ward, W. H., and Fevold, H. L.: Isolation of Lysozyme From Egg White, J. Biol. Chem. **157**: 43-58, 1945.
41. Ingvaldsen, T., Whipple, A. O., Bauman, L., and Smith, B. C.: The Role of Anhydremia and the Nature of the Toxin in Intestinal Obstruction, J. Exper. Med. **39**: 117-127, 1924.
42. Tanturi, C. A., Anderson, R. E., and Canepa, J. F.: Lecithinase and Hyaluronidase in Experimental Intestinal Obstruction, Surg., Gynec. & Obst. **90**: 171-174, 1950.
43. Anderson, R. E., and Tanturi, C. A.: Identification of the Toxin of Clostridium Organisms in Experimental Intestinal Obstruction, Arch. Surg. **60**: 143-153, 1950.
44. Cole, F., Baronofsky, I. D., and Wangensteen, O. H.: Curare and Shock: The Production of Hemorrhage Into the Upper Intestine of the Dog With Large Doses of Curare, SURGERY **21**: 881-888, 1947.
45. Dragstedt, L. R., Moorhead, J. J., and Burcky, F. W.: Intestinal Obstruction. An Experimental Study of the Intoxication in Closed Intestinal Loops, J. Exper. Med. **25**: 421-439, 1917.

EVIDENCE FOR A RENAL FACTOR IN THE HYPERTENSION OF EXPERIMENTAL COARCTATION OF THE AORTA

H. William Scott, Jr., M.D., and Henry T. Bahnson, M.D., Baltimore, Md.

(From the Surgical Hunterian Laboratory of the Johns Hopkins University School of Medicine)

THE mechanism of the elevated arterial pressure in coarctation of the aorta has been the subject of much speculation and investigation. In general there are 2 opposing views concerning the cause of hypertension in this disorder. The first and most obvious explanation was offered by Blumgart and associates[1] in 1931. These authors suggested that the hypertension resulted from resistance to blood flow presented by the aortic stricture itself and the collateral vessels. Bing and co-workers[2] have recently supported this view by a study of the peripheral resistance in patients with coarctation. The second hypothesis, proposed by Steele,[3] Rytand,[4] Stewart and Bailey,[5] Page,[6] and others, is that there is a generalized increase in vascular resistance due to disturbance of renal hemodynamics.

We have investigated this problem by a study of the development of hypertension in dogs with experimentally produced coarctation of the aorta and by observations of the effects of transplanting the kidney to a level above the coarctation.

METHODS

Various experimental techniques have been devised in an effort to produce extensive stenosis or complete occlusion of the thoracic aorta in surviving animals. The work of Halsted,[7] Reid,[8] Matas and Allen,[9] Pearse,[10] Owings,[11] and others indicated the necessity for bringing about the occlusion gradually. Sudden complete occlusion of the aortic isthmus is not compatible with long survival in experimental animals.

In preliminary experiments we attempted to bring about constriction of the aortic isthmus by the use of cellophane as described by Pearse, but the insignificant degree of stenosis obtained in a small number of animals caused us to abandon this method. Another method which was tried and discarded consisted in the use of powdered metallic magnesium[12] applied circumferentially to the aortic isthmus and maintained in close apposition by an encircling cellophane band. Again no significant stenosis resulted in the few animals studied. The procedure which was finally adopted for use in this study is a modification of the operation devised by Blalock and Park[13] for circumventing the stenotic area in patients with coarctation by anastomosis of the left subclavian artery to the side of the aorta distal to the point of stenosis.

The operative technique as carried out in dogs in these experiments was as follows: After morphine and atropine premedication the animal was anesthetized with ether. Pulmonary ventilation was maintained by the use of an intratracheal tube and a mechanical insufflator.[14] Using aseptic technique an incision

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was made in the 4th left intercostal space. The aortic isthmus and the left subclavian artery were mobilized. Usually the first pair of aortic intercostal arteries was divided.

A Potts aortic clamp was used to occlude partially the aorta and allow the construction of a suture anastomosis between the end of the left subclavian artery and the side of the aorta as far below the origin of the left subclavian as length of the latter allowed. After completion of this anastomosis the aorta was divided between Potts ductus clamps placed adjacent to the origin of the subclavian above and the anastomosis below. The aortic ends were closed with 2 rows of continuous silk and the 2 ends were sutured together to prevent retraction. After the anastomosis a thrill and a faint pulse were palpable in the

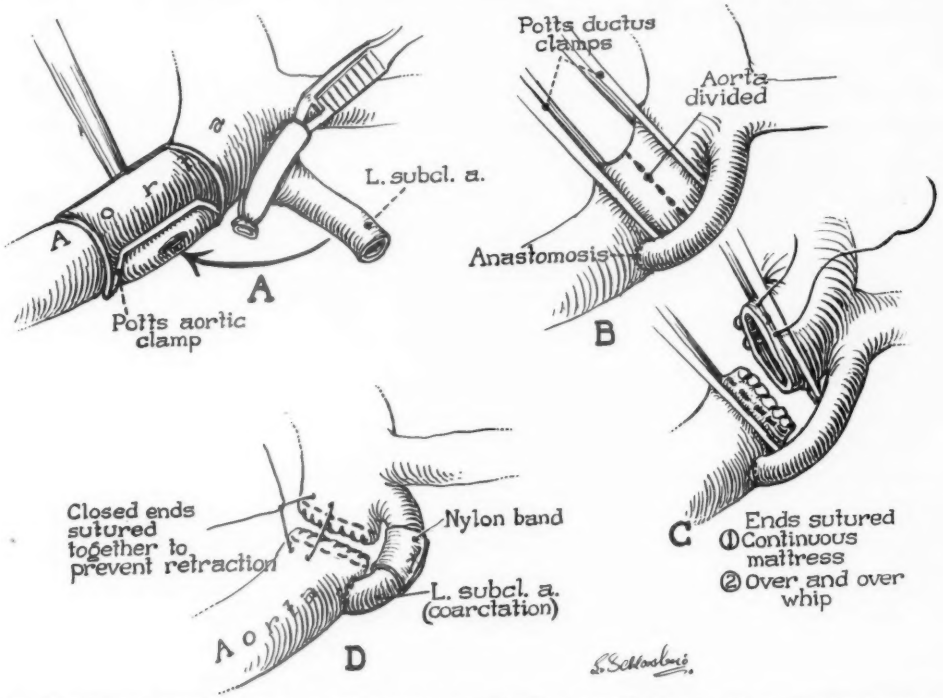


Fig. 1.—Method of production of experimental coarctation (modification of operation devised by Blalock and Park). *A, B, C,* and *D,* sequence of technical steps.

thoracic aorta. A band of treated nylon* 5 mm. in width was drawn around the left subclavian artery and sutured snugly but without constriction of the vessel. The steps in technique are sketched in Fig. 1.

This technique offers the advantages of a one-stage procedure which can be employed in adult dogs as well as puppies. A fairly uniform degree of stenosis of the aortic isthmus is produced and observations of a comparable nature may be made in a series of animals. Since the aortic flow is never completely interrupted, hind leg paralysis is not a significant postoperative complication in these preparations. The disadvantages of the method are related to the fairly elaborate technical procedure and the hazards of rupture of the aorta or thrombosis of the small subclavian-aortic anastomosis.

*Prepared at the suggestion of Dr. Mark Kai-Hsi Wang by immersing thin nylon cloth in a solution of cleared radiographic film in acetone.

This procedure has been employed in 58 dogs. Heavy losses were sustained in the initial experiments due to faulty anesthesia and operative technique, distemper, rupture of the aortic closure, and thrombosis of the anastomosis. Twenty-three animals survived for a period of 1 month or longer.

In 8 of the surviving dogs we attempted to produce complete obstruction of the aorta by dividing the interpolated subclavian artery at a second operation 3 weeks to 2 months after the initial procedure. Only 2 animals tolerated ligation of the subclavian artery. The remaining 6 dogs died in the immediate postoperative period with hind leg paralysis, pulmonary edema, and anuria. The operations upon the 2 surviving animals were performed at intervals of 6 weeks and 2 months. Preoperative digitalization and postoperative whole blood transfusions were thought to be of value in these 2 animals. Neither dog developed hind limb paralysis.

From these preliminary experiments it became apparent that the animals were developing hypertension following the initial procedure and that secondary ligation of the interpolated subclavian artery was not necessary. The subsequent experiments were devoted to a study of the development and course of the hypertension.

In 15 dogs which survived the operative procedure, studies of arterial pressure were made for periods of 2 to 10 months. Diet consisted of daily feedings of chow.* Water was not restricted. At least a week prior to thoracotomy the right carotid artery was transplanted to a subcutaneous position to facilitate subsequent needle puncture.

Blood pressure was determined without anesthesia by direct puncture of the femoral and carotid arteries using a No. 20 gauge needle attached to a mercury manometer. Arterial pressures were intermittently measured and recorded by a Sanborn electromanometer or a Hathaway oscillograph. Mean pressures were recorded on the electromanometer by the electrical integrator, and were estimated on the oscillograph by planimetric integration of the area under the pressure curve.

Pressures in the carotid and the femoral artery of each dog were determined by repeated measurements over a 3- to 10-day period before the production of coarctation. Animals with pressures persistently over 150 mm. Hg were excluded. Pressures in the femoral and carotid arteries were measured frequently in the first 3 to 4 weeks after the production of coarctation and thereafter at weekly intervals for periods ranging up to 10 months.

To clarify the role of the kidney in the hypertension of coarctation a kidney was transplanted to the neck in 8 dogs after hypertension was established. The Carrel technique[15] was employed. The external jugular vein and the carotid artery were mobilized through a vertical incision in the left side of the neck. The left kidney was approached through an incision in the loin. The renal vessels and ureter were divided and as much length as possible was obtained of the renal artery and vein. A suture anastomosis was made between the ends of the carotid and renal arteries and of the external jugular and renal veins.

*Friskies Dog Food (Meal), Carnation Company, New York.

The end of the ureter was exteriorized, and a short length of Polythene tubing was inserted into the end and tied in place. The edges of the cervical wound were undermined to make a bed for the kidney prior to closure of the incision (Fig. 2). In each experiment the contralateral kidney was removed. In a few instances this was done at the time of the renal transplantation and in others 3 to 7 days later. All dogs were given penicillin and streptomycin for 5 to 7 days after operation.

To serve as control experiments for the cervical transplantations a kidney was transplanted to the groin in 5 dogs with coarctation by the method of Glenn, Child, and Heuer.[16] A long right paramedian incision was made and the external iliac vessels were mobilized. The right kidney was freed and its vessels were divided close to the aorta and vena cava. The ureter was left attached to the

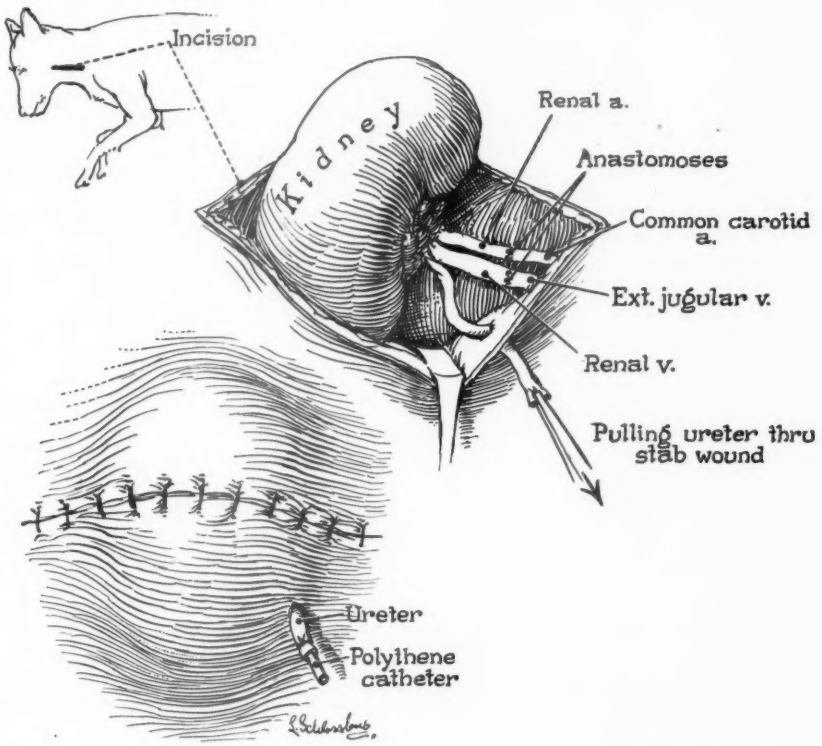


Fig. 2.—Method of cervical renal transplantation used in this study (Carrel).

bladder but was mobilized sufficiently to permit the kidney to be placed in the groin in apposition to the iliac vessels. End-to-end suture anastomoses were performed. The inguinal ligament was divided and the kidney placed beneath the skin in the groin. Peritoneum and abdominal musculature were closed loosely about the renal pedicle. Antibiotics and removal of the contralateral kidney were employed as in the previous group of experiments.

RESULTS

In general, animals with experimental coarctation which survived the operative and immediate postoperative difficulties remained healthy and active. One

of the 23 survivors developed a transitory paralysis of the hind limbs immediately after operation. Because of hemorrhage during this operation it had been necessary to occlude the aorta completely for about 10 minutes. None of the other dogs showed any conspicuous weakness and none developed other abnormalities, excepting one dog which died of distemper.

Fig. 3.—Photograph of segment of aorta of a dog autopsied 2 months after production of experimental coarctation. Note dense scar around interpolated subclavian artery.

Autopsy was performed on 15 dogs after survival periods of 1 to 10 months. In 13 of these the anastomosis was patent and functioning satisfactorily to produce a coarctate area (Fig. 3). In one dog the subclavian artery was completely occluded by thrombus. Another animal was found to have an aneurysm which had ruptured from the upper to the lower aortic segment causing a communication about 1 cm. in diameter. (This animal is the only one in the series which did not develop hypertension and it was eliminated from the study after postmortem examination.) There was usually some constriction at the anastomosis and in 3 animals the lumen was reduced to a diameter of 1 to 3 mm. There was

extensive fibrosis around the subclavian artery at the site of the nylon band in each case. The efficacy of the nylon was never clarified. It is our impression that the scarring which was produced prevented dilatation of the subclavian artery. Certainly in the group of dogs in which the subclavian artery was later divided the nylon served as a convenient landmark in the mass of scar. Measurements of the mid-portion of the subclavian artery and of the aorta immediately distal to the anastomosis were made at autopsy on 6 dogs. These showed that interposition of the subclavian caused an average reduction of 79 per cent in the

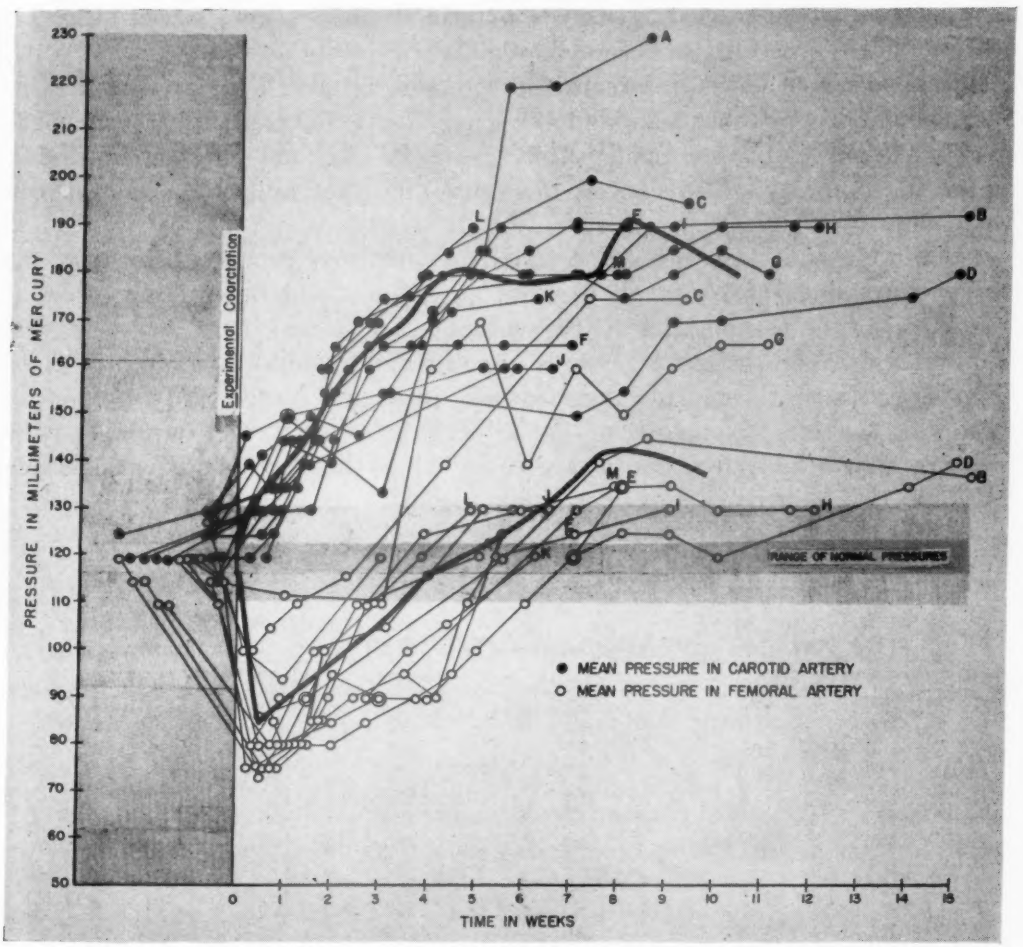

PRESSURE IN MILLIMETERS OF MERCURY
TIME IN WEEKS
Experimental Coarctation
RANGE OF NORMAL PRESSURES
MEAN PRESSURE IN CAROTID ARTERY
MEAN PRESSURE IN FEMORAL ARTERY

Fig. 4.—Graph showing development of hypertension in 13 dogs with experimental coarctation of the aorta. Heavy lines are calculated mean curves of carotid and femoral pressures.

cross-sectional area of the aortic isthmus. The degree of reduction ranged from 66 to 94 per cent. In several instances the anastomosis was responsible for even further constriction.

Preoperative control measurements of mean pressures in femoral and carotid arteries fell into a range between 110 and 130 mm. Hg. The carotid pressure was frequently, though not always, 5 to 10 mm. Hg higher than the femoral. After the production of coarctation there was a greater disparity in

the 2 pressures in all animals. The femoral fell to 57 to 73 per cent of the carotid pressure and ranged from 70 to 120 mm. Hg in the first 72 hours. During this time the carotid pressure showed little or only a slight rise (0 to 18 mm. Hg) from preoperative levels. In one animal the carotid pressure was 60 mm. Hg higher than the control measurements when first taken 72 hours after operation; the femoral pressure showed a rise of 5 mm. Hg. Marked excitement in this dog was thought to be a major factor in the cervical hypertension at this time.

There was a gradually progressive rise in the mean carotid pressure following operation which seemed to reach a plateau in about 5 to 7 weeks (Fig. 4). To state when hypertension occurred would be to invite an argument as to the definition of hypertension. Except for the one excitable dog previously mentioned, none of the animals showed elevations above 150 mm. Hg, a commonly accepted upper limit of normal, before the ninth day, and all showed it after the twenty-first day. The slope of the curve, however, indicates that the rise began immediately.

Similarly, the mean femoral arterial pressure rose progressively after the initial depression. After about 6 weeks all animals had femoral pressures at least equal to the preoperative control values and 7 showed more than a 10 mm. Hg increase. The disparity between carotid and femoral pressures in these animals persisted throughout their course, although it decreased in quantity (Table I). From the records of the arterial pressure it was seen that pulse pressure above the coarctation was greater, while that below was considerably less than that noted prior to operation (Fig. 5).

TABLE I. MEAN ARTERIAL PRESSURES AFTER EXPERIMENTAL COARCTATION

DOG	FIRST 72 HOURS AFTER OPERATION		CAROTID/FEMORAL RATIO	PRIOR TO ATTEMPTED RENAL TRANSPLANTATIONS†		CAROTID/FEMORAL RATIO
	CAROTID	FEMORAL		CAROTID	FEMORAL	
A	142	86	.61	185	120	.65
B	130	80	.62	195	140	.72
C	140	100	.71	195	175	.90
D	146	106	.73	175	135	.77
E	125	75	.60	190	135	.71
F	125	80	.64	160	125	.78
G	180*	120*	.60	185	150	.81
H	140	80	.57	185	125	.68
I	120	75	.63	190	130	.68
J	120	75	.62	160	125	.78
K	130	75	.58	175	120	.69
L	125	75	.56	185	130	.70
M	130	75	.58	180	135	.75

*Dog very excited.
†One to 4 months after production of coarctation.

Successful cervical renal transplantation with contralateral nephrectomy was achieved in 5 of the 8 dogs with coarctation in which this was attempted. One dog died with a cervical wound infection and rupture of the renal arterial anastomosis 2 weeks after renal transplantation. The other 4 dogs lived for 1, 2, 3, and 4 months, respectively. Each of these animals ultimately died with ureteral obstruction and pyelonephritis.

In all 5 of these animals there was a prompt reduction in mean pressure in both carotid and femoral arteries. Seven days after renal transplantation no animal had a carotid pressure above 140 mm. Hg, and by the third week mean carotid pressures in the 4 surviving dogs had fallen to levels equal to or below the normal levels observed before the production of coarctation (Fig. 6). The disparity in the levels of mean femoral and carotid pressures persisted.

Nonprotein nitrogen of the plasma was persistently elevated in these animals, ranging from about 60 to 90 mg. per cent. These values remained fairly stable, however, until terminal uremia began.

One of 5 animals with hypertension established by coarctation has survived a transplantation of a kidney to the groin with subsequent contralateral nephrectomy, and has been observed for 4½ months. This animal has shown no change in arterial pressure since this form of renal transplantation, and the hypertensive pattern of coarctation persists.

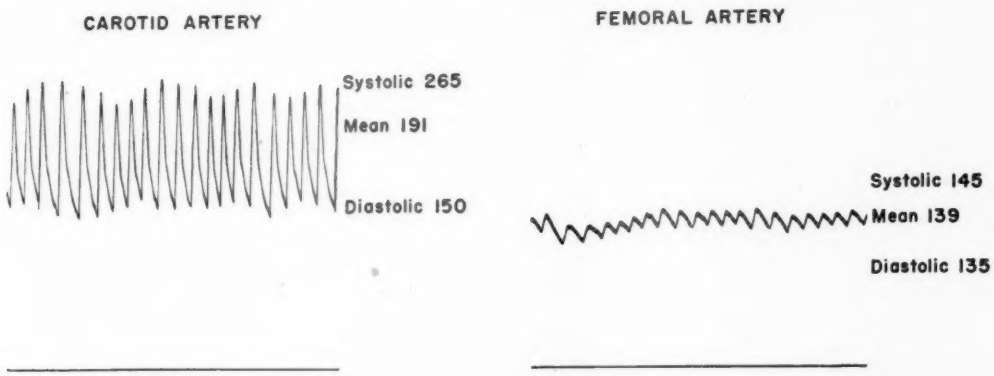


Fig. 5.—Pressure tracing (Hathaway oscillograph) from animal in this study 2 months after production of experimental coarctation.

COMMENT

The method of production of experimental coarctation used in these studies in dogs results in anatomic and hemodynamic alterations which resemble those of human coarctation. The degree of stenosis of the aortic isthmus which is produced is similar to that achieved with the techniques described by Clatworthy,[17] Sealy,[18] Gerbode,[19] and their respective associates.

Studies of arterial pressures in animals with experimental coarctation show an immediate fall in mean femoral pressure after operation, which is followed by a slow rise to normal, and in some instances, supranormal levels. There is a gradually progressive rise in mean carotid pressure which reaches a hypertensive plateau 5 to 7 weeks after the operation.

These findings are similar to those of Sealy and McSwain[18] in their studies of experimental coarctation. As pointed out by Sealy, a purely mechanical theory of the origin of hypertension in coarctation is not supported by these observations. If the mechanical effects of the aortic stenosis were the sole cause

of the hypertension, one would logically expect the maximum elevation in carotid pressure to be attained shortly after the production of experimental coarctation and to decline gradually thereafter with improvement in collateral circulation. Our data show that this does not occur. In addition, the observed rise in femoral pressure to supranormal levels in some of the animals is difficult to conciliate with the purely mechanical hypothesis.

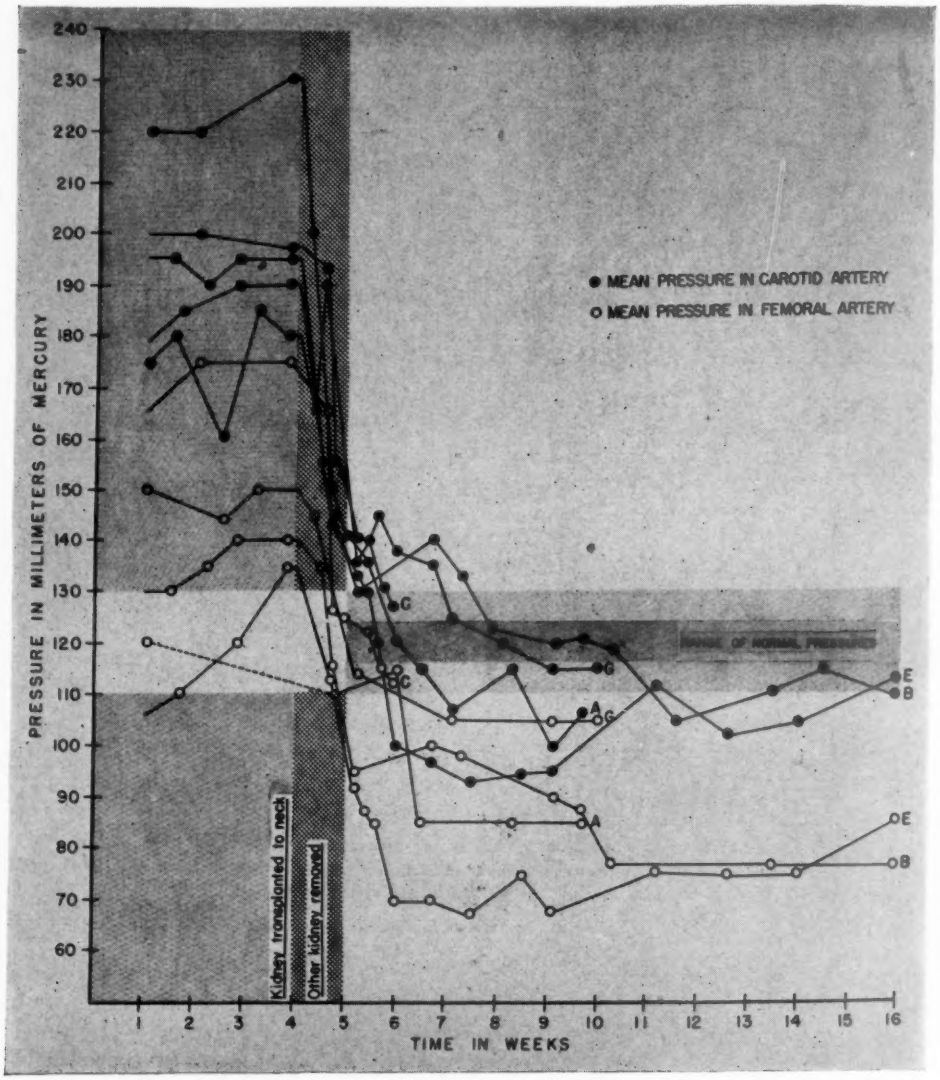


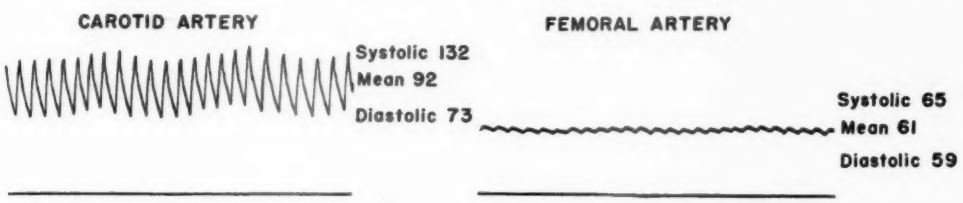
Fig. 6.—Graph showing disappearance of hypertension after cervical renal transplantation and contralateral nephrectomy in 5 dogs with experimental coarctation.

The changes in arterial pressures which occur in dogs after transplantation of a kidney to a level above the site of coarctation offer additional evidence that the mechanical hypothesis is inadequate. The disappearance of hypertension observed consistently in these animals with all functioning renal tissue above the aortic stricture suggests the action of a mechanism in experimental coarctation

which is similar to that of the Goldblatt kidney. A mechanical effect of experimental coarctation in these dogs is illustrated by the disparity in carotid and femoral pressures after the disappearance of hypertension (Fig. 7). The successful control experiment indicates that the hypertensive pattern of experimental coarctation is not affected by transplantation of a kidney to the groin. Additional control experiments are in progress, but we suspect that the low mean and pulse pressure in the femoral artery is an important cause of failure in attempts to transplant a kidney to the groin.

These studies strongly suggest that the hypertension of experimental coarctation is of renal origin. It seems likely that the mechanical effect of the aortic stenosis serves as the stimulus to renal hypertension by altering the hemodynamics below the aortic isthmus. This hypothesis has been advocated by Rytand,[4] Steele,[3] Page,[6] and others, and is supported by much of the previous work in this field.

Goldblatt and associates[20] have shown that constriction of the abdominal aorta in dogs above the level of the renal arteries results in hypertension while constriction below this level does not. Page[6] was unable to produce hypertension



EXPERIMENTAL COARCTATION
AFTER TRANSPLANTATION OF KIDNEY TO NECK

Fig. 7.—Pressure tracing (Hathaway oscillograph) from animal, whose earlier tracing is shown in Fig. 5, one month after cervical renal transplantation and contralateral nephrectomy.

in dogs by constriction of the aortic isthmus with a metal clamp. In his experiments, however, the dogs died from erosion of the aortic wall and hemorrhage within 3 to 12 days after application of the clamp. Our studies and those of Sealy and McSwain[18] show that manifest hypertension is usually not observed until 9 to 12 days after the production of experimental coarctation by methods compatible with long survival of animals.

Studies of peripheral resistance in patients with coarctation have produced evidence both for[3, 5] and against[2] a renal factor in the hypertension. Harris and associates[21] have recently pointed out the inconclusive nature of this evidence and errors inherent in studies of this type.

Investigation of renal dynamics in patients with coarctation by Friedman[22] and Genest[23] and their respective co-workers has indicated that the renal pattern is similar to that found in essential hypertension. However, on the basis of similar studies in clinical as well as experimental coarctation Harris and his group[21] found it impossible to ascribe the etiology of the hypertension to renal ischemia. At the same time these authors suggested that the low pulse pressure below the aortic constriction may serve as the stimulus to the production of

renin. It should be pointed out that the brachiocephalic hypertension of coarctation may function to maintain an adequate renal blood flow. If so, one would not expect to find a reduced flow by direct or indirect measurements.

Our observations indicate that the hypertension of experimental coarctation is mediated through a renal mechanism. This mechanism is inactivated by transplantation of a kidney to the vascular system above the coarctation. Whether or not these observations have implications for clinical coarctation can only be decided by further investigation.

SUMMARY

A study was made of the hypertension in dogs with experimental coarctation of the aorta. A gradually progressive rise in carotid pressure was observed which reached a hypertensive plateau 5 to 7 weeks after the production of coarctation. There was an immediate fall in femoral pressure after operation, which was followed by a slow rise to normal and, in some instances, supranormal levels. Transplantation of a kidney to a level above the coarctation and contralateral nephrectomy resulted in disappearance of hypertension in 5 animals with experimental coarctation. No change in hypertension occurred in another animal with coarctation when a kidney was transplanted to the groin and contralateral nephrectomy performed. These studies suggest that the hypertension of experimental coarctation is mediated through a renal mechanism.

REFERENCES

1. Blumgart, H. L., Lawrence, J. S., and Ernestene, A. C.: The Dynamics of the Circulation in Coarctation of the Aorta of the Adult Type, Arch. Int. Med. **47**: 806, 1931.
2. Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E., and Blalock, A.: The Surgical Treatment and the Physiopathology of Coarctation of the Aorta, Ann. Surg. **128**: 803, 1948.
3. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta, J. Clin. Investigation **20**: 473, 1941.
4. Rytand, D. A.: The Renal Factor in Arterial Hypertension With Coarctation of the Aorta, J. Clin. Investigation **17**: 391, 1938.
5. Stewart, H. J., and Bailey, R. L.: The Cardiac Output and Other Measurements of the Circulation in Coarctation of the Aorta, J. Clin. Investigation **20**: 145, 1941.
6. Page, I. H.: The Effect of Chronic Constriction of the Aorta on Arterial Blood Pressure in Dogs: An Attempt to Produce Coarctation of the Aorta, Am. Heart J. **19**: 218, 1940.
7. Halsted, W. S.: Partial Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band, J. Exper. Med. **11**: 373, 1911.
8. Reid, M. R.: Partial Occlusion of the Aorta With Silk Sutures and Complete Occlusion With Fascial Plugs: The Effect of Ligatures on the Arterial Wall, J. Exper. Med. **40**: 293, 1924.
9. Matas, R., and Allen, C. W.: Conclusions Drawn From an Experimental Investigation Into the Practicability of Reducing the Caliber of the Thoracic Aorta by a Method of Plication or Infolding of Its Walls by Means of a Lateral Parietal Suture Applied in One or More Stages, Ann. Surg. **58**: 304, 1913.
10. Pearse, H. E.: Experimental Studies on the Gradual Occlusion of Large Arteries, Ann. Surg. **112**: 923, 1940.
11. Owings, J. C.: Successful Experimental Ligation and Division of the Thoracic Aorta, Ann. Surg. **115**: 596, 1942.
12. Schulz, R. Z., and Walter, C. W.: Magnesiogenous Pneumagranuloma, J. Indust. Hyg. & Toxicol. **24**: 148, 1942.
13. Blalock, A., and Park, E. A.: Surgical Treatment of Experimental Coarctation of the Aorta, Ann. Surg. **119**: 445, 1944.
14. Hanlon, C. R., Johns, T. N. P., and Thomas, V.: An Apparatus for Anesthesia in Experimental Thoracic Surgery, J. Thoracic Surg. **19**: 887, 1950.
15. Carrel, A.: The Ultimate Results of Double Nephrectomy and Replantation of One Kidney, J. Exper. Med. **14**: 124, 1911.

16. Glenn, F., Child, C. G., and Heuer, G. J.: Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney, Ann. Surg. **106**: 848, 1937.
17. Clatworthy, H. W., Jr., Sako, Y., Chisholm, T. C., Culmer, C., and Varco, R. L.: Thoracic Aortic Coarctation, SURGERY **28**: 245, 1950.
18. Sealy, W. C., and McSwain, G. H.: A Method for Producing Coarctation of the Thoracic Aorta in Dogs, SURGERY **25**: 451, 1949.
19. Gerbode, F.: Discussion of paper by Clatworthy and associates.[17]
20. Goldblatt, H., Kahn, J. R., and Hanzal, R. F.: Studies on Experimental Hypertension IX. The Effect on Blood Pressure of Constriction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries, J. Exper. Med. **69**: 649, 1939.
21. Harris, J. S., Sealy, W. C., and DeMaria, W.: Hypertension and Renal Dynamics in Aortic Coarctation, Am. J. Med. **9**: 734, 1950.
22. Friedman, M., Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Coarctation of the Aorta, J. Clin. Investigation **20**: 107, 1941.
23. Genest, J., Newman, E. V., Kattus, A. A., Sinclair-Smith, B., and Genecin, A.: Renal Function Before and After Surgical Resection of Coarctation of the Aorta, Bull. Johns Hopkins Hosp. **83**: 429, 1948.

DISCUSSION

DR. WILL C. SEALY.—I want to congratulate Dr. Scott on a very ingenious method of producing coarctation, which is a very difficult experimental preparation to produce. We have felt very confident that there was not a renal factor in the mechanism of hypertension, as we had done studies on patients in much detail before and after operation, and we had found that these studies before operation were certainly not markedly abnormal, perhaps a little low in renal blood flow. However, immediately after operation within the first 7 days there was a rather marked increase in renal blood flow, and we thought for the moment that that was probably the answer—that it was renal in origin. Studies on these same patients from 30 to 90 days afterward showed that their renal clearance studies reverted to normal and were back at the preoperative level.

We have tried to do this same work on dogs, but it is extremely difficult to do adequate clearance studies in animals. They vary so tremendously from animal to animal. But certainly as far as the indirect measurement of renal blood flow, we never could demonstrate that experimental coarctation produced any marked decrease in renal blood flow other than in the first few days, nor could we show any correlation in the renal blood flow and the filtration rate and the development of hypertension. The work of Dr. Scott, I think, has made it evident that further work will have to be done to rule out a renal factor in the development of hypertension of coarctation of the aorta.

DR. HARRIS B. SHUMACKER, JR.—I also would like to congratulate Dr. Scott on this perfectly beautiful experimental work. As Dr. Sealy mentioned, the results of renal clearance studies in patients with coarctation made before and after surgical treatment are rather puzzling and difficult to interpret. We have, with the help of Dr. Kohlstaedt and his associates, done such studies on a number of individuals with coarctation and in most of them there has been no very striking alteration after operative correction of the coarctation. However, in one patient who had very evident diminution of renal function before operation, having some papilledema, some elevation in nonprotein nitrogen, depression of the usual renal function tests, as well as markedly reduced renal clearance studies, there was a correction of all these difficulties after operation: prompt subsidence of the papilledema, prompt drop to normal of nonprotein nitrogen, very marked increase in renal blood flow. Why such observations are made in such a small percentage of patients, I do not know.

DR. H. WILLIAM SCOTT, JR. (Closing).—I would like to thank Dr. Sealy and Dr. Shumacker for their remarks. There is only one other thing that I would like to say. Recently Dr. Bahnson and I had a teleological thought in this regard and we wondered why it had not been suggested before in relation to the problem of renal hemodynamics in coarctation of the aorta; and that is the possibility that the brachiocephalic hypertension may serve to maintain an adequate renal blood flow below the aortic constriction. If it does, then one would not expect a reduction in renal blood flow by any form of measurement.

THE SUPERSENSITIVITY OF DENERVATED DIGITAL BLOOD VESSELS IN MAN

F. A. Simeone, M.D., Cleveland, Ohio, and (by invitation)
D. A. Felder, M.D., Minneapolis, Minn.

(From the Surgical Research Laboratories of the Harvard Medical School at the Massachusetts General Hospital, Boston, Mass., and the Department of Surgery of Western Reserve University Medical School at City Hospital, Cleveland, Ohio)

TELFORD[33] and Smithwick[29] devised techniques for effecting a preganglionic type of denervation for the treatment of vasospastic conditions of the upper extremities. The desirability of producing a preganglionic as opposed to a postganglionic type of denervation was based upon the observation in animals[20] that after the former procedure smooth muscle becomes much less sensitive to chemical stimuli than after the latter. Freeman and associates[17] and Smithwick and co-workers[30] had presented evidence in man that after postganglionic denervation blood vessels are extraordinarily sensitive to injected adrenaline or secreted adrenine. White, Okelberry, and Whitelaw[34] pointed out that, unlike the situation in the upper extremities, the usual lumbar ganglionectomy actually resulted in a preganglionic denervation for the lower extremities. They postulated that this difference might account for the difference in the results of sympathectomy for vasospastic states of the upper and lower extremities, respectively. Ascroft[1] demonstrated that the conversion of a preganglionic to a postganglionic type of denervation of the lower extremities increased the responsiveness of the blood vessels to adrenaline.

Since these early studies, several investigators have observed that recurrence of vasospasm almost never occurs without the presence of demonstrable vasomotor nervous activity.[3, 4, 15, 21, 28, 31] These observations would minimize the significance of supersensitivity for the recurrence of vasospasm after sympathetic denervation, and, more recently, the physiologic significance of the phenomenon itself has been questioned.[23] Because of this state of confusion of the problem, it was thought desirable to present further data on the occurrence of postdenervation supersensitivity of blood vessels in man and to discuss its implications.

METHOD

The sensitivity of the digital blood vessels to adrenaline was studied in 20 patients who had abnormal vasospasm in the digits upon exposure to cold (Raynaud's phenomenon). The tests were done in a constant temperature room at 20° to 21° C., with and without heating of the trunk by means of a heat cradle, or with the room at 33° C. At the time of the tests, the extremities studied had been denervated either chronically by operation or acutely by blocking the appropriate peripheral nerves with procaine. Three of the 20 patients did not have sympathectomy and served as controls. One patient had sympathectomy for the lower extremities only, with excision of the first, second, and third lumbar ganglia bilaterally. Sixteen had denervations of the upper

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extremities, 2 of them only unilaterally so that a total of 30 chronically denervated upper extremities were studied. In none of the patients was this denervation completely postganglionic. In only 3 patients, who had had resections including the first thoracic and inferior cervical ganglia, could the denervation have been largely postganglionic, and for the remainder, the denervations were largely preganglionic. From material such as this, it is obvious that while it may be reasonable to look for postdenervation supersensitivity, it would be futile to try to demonstrate a difference between the effects of preganglionic and postganglionic denervation.

Only 5 patients were studied both before and after sympathectomy; 7 were studied before, and 15 were studied after operation. The postoperative tests were done at intervals of 3 days to 4 weeks, at 4 months, at 6 months, and at 1 year after operation. Among 15 patients who were studied 4 months or more after sympathectomy, 11 showed signs of residual or recurrent vasomotor activity. This was abolished by means of procaine injection of the peripheral nerves except in 3 patients who were studied both with and without the blocks for specific reasons.

Observations on the responsiveness of the digital blood vessels to adrenaline were made by recording the changes in digital volume by means of the Burch-Winsor plethysmograph and by noting the changes in the color of the skin. Continuous records were made of the digital skin temperature during these tests, but, with the technique used, no significant changes were observed as the result of the single injections of adrenaline. The plethysmograms were prepared and processed as described by Burch.[5] All injections of adrenaline were made into the cephalic or basilic vein at the elbow through the side arm of a three-way stopcock in an intravenous infusion apparatus. The flow was adjusted to 4 c.c. per minute. The dosage was 4.4 γ of adrenaline diluted to 2.0 c.c. in isotonic saline solution and injected in approximately 10 seconds. The subject was never aware of the time the injection was made and controls were obtained by injecting saline solution alone or by slow and deliberate manipulation of the apparatus as if an injection was being made. Six to 10 minutes were allowed to elapse between injections, and 2 to 5 consecutive tests were done for each digit studied, recording with the plethysmograph from opposite sides with successive injections.

RESULTS

1. *Color Changes in the Skin After Intravenous Injections of Adrenaline.*—The effect of injections of single doses of adrenaline intravenously (4.4 γ in 10 seconds) upon the color of the skin was studied in all 20 patients. As many as 50 observations were done in individual patients at several study periods 3 days to 1 year after operation. Nonsympathectomized extremities were studied in 10 patients; sympathectomized extremities were studied in 17 patients, 30 upper extremities and 2 lower extremities. Among these 17 patients there were signs of recurrence of vasomotor activity in 15 upper extremities. There was no evidence of return of vasomotor activity in the 1 patient of this group who had had bilateral lumbar ganglionectomy.

The observations are recorded in Table I. It is apparent that both in the warm room and in the cold room, single doses of adrenaline injected intravenously produced paling in only about one-fourth of the individuals, even when exposed in a cool environment (20° to 21° C.). When observed, the paling was of minor degree, diffuse, and did not resemble the circumscribed pallor seen during attacks characteristic of Raynaud's disease.

Cyanosis of the digits developed in only one case (Table I). This was a patient who had demonstrable vasomotor recurrence after sympathectomy and, as a matter of fact, the cyanosis did not appear until after the procaine nerve block had begun to wear off.

TABLE I. COLOR CHANGES OF DIGITS IN RESPONSE TO ADRENALINE INJECTED INTRAVENOUSLY BEFORE AND ONE TO SIX MONTHS AFTER SYMPATHECTOMY

RELATION TO SYMPATHECTOMY	NUMBER OF OBSERVATIONS (IN 20 PATIENTS)		NUMBER PATIENTS DEVELOPED PALLOR		NUMBER PATIENTS DEVELOPED CYANOSIS	
	COLD ROOM	WARM ROOM	COLD ROOM	WARM ROOM	COLD ROOM	WARM ROOM
Before sympathectomy; vasomotor activity blocked by procaine injection (10 patients)	66	56	4	4	0	0
After sympathectomy without vasomotor recurrence (17 extremities in 12 patients)	42	88	3	4	0	0
After sympathectomy with vasomotor recurrence blocked by procaine (15 extremities in 11 patients)	23	55	2	3	1	0
Total	131	199	9	11	1	0

It is important to note here that cyanosis or blanching did develop uniformly among individuals who had demonstrable vasomotor activity, were not blocked with procaine, and had adrenaline injected intravenously in single doses. The adrenaline injection, of course, was usually unnecessary in a group of patients such as this since most of them, though not all, developed cyanosis and some developed blanching when merely exposed to cold in individual tests.

TABLE II. AVERAGE DECREASE IN DIGITAL VOLUME IN RESPONSE TO ADRENALINE INJECTED INTRAVENOUSLY

PATIENT	AGE	SEX	SIDE	BEFORE OPERATION		AFTER OPERATION (ONE WEEK OR MORE)	
				NO. OF TESTS	AVERAGE RESPONSE (C.MM. PER 5 C.C. OF PART)	NO. OF TESTS	AVERAGE RESPONSE (C.MM. PER 5 C.C. OF PART)
P. M.	19	F	Right	3	19.5	4	56.3
			Left	1	33.0	7	58.6
C. D'A.	30	F	Right			5	86.6
			Left	3	50.5	2	83.7
W. H.	39	M	Right	2	32.9	10	95.5
			Left	4	33.8	5	100.3
H. B.	44	F	Right	2	34.5	1	91.0
			Left			2	94.5
A. H.	52	F	Right	6	42.5	2	94.5
			Left	3	61.8	6	92.3
Total				24	38.6	44	Average 85.3

2. *Plethysmographic Responses of the Digits to Adrenaline Injected intravenously in Single Doses.*—The responses of the fifth digit before and after sympathetic denervation were studied in 8 extremities in 5 patients. The results are presented in Table II. The data indicate that for individual patients, as well as for averages of all 5, the responses to single intravenous injections of adrenaline were greater after sympathectomy than before. The average digital contraction was twice as great in the chronically denervated fingers than in the same fingers before sympathectomy and released from vasomotor control by procaine block of the peripheral nerves. Fig. 1 illustrates a typical response of the same digit before operation (circles) and 4 weeks after sympathetic denervation (dots). In this case, the denervation had been accomplished by excision of the second and third thoracic ganglia and intraspinal section of the roots of the second and third intercostal nerves, presumably a preganglionic denervation for the most part. The difference between the 2 curves is obvious.

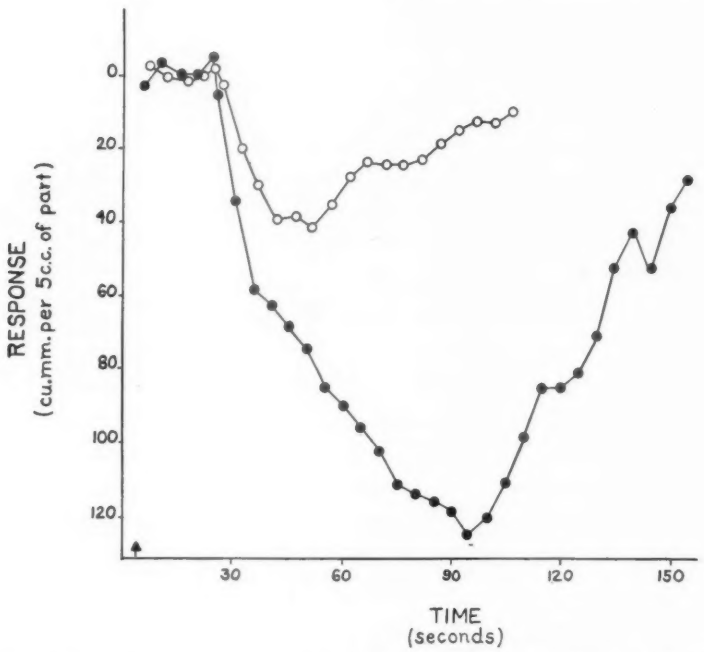

Fig. 1.—Curves representing the shrinkage of the terminal phalanx of the fifth finger (volume 4.5 c.c.) before (circles) and 4 weeks after (dots) sympathetic denervation. The points are taken from a plethysmograph record at 5 second intervals. All values are corrected and expressed as cubic millimeters per 5 c.c. of part. Ordinate: cubic millimeters per 5 c.c. of part; abscissa: time in seconds.

DISCUSSION

In the preceding experiments it has been impossible to produce the circumscribed pallor of Raynaud's disease or the cyanosis of Raynaud's phenomenon in the absence of vasomotor activity. The doses used were sufficiently great to induce facial pallor and subjective symptoms in all cases. By using larger and subcutaneous doses of adrenaline or by inducing sympathico-adrenal activity by means of insulin hypoglycemia, Heinbecker and Bishop[22] were able to cause cyanosis in patients with vasospastic disease before sympathectomy but

not in normal individuals. These observations are not sufficiently discriminative to determine whether or not the fault in so-called Raynaud's disease lies in a supersensitive effector or in an overactive sympathico-adrenal system. They do indicate that functioning vasoconstrictor nerves are of major importance for the production of clinical vasospasm and that recurrences after sympathectomy are conditioned by their presence.

In the five patients who were studied both before and after sympathectomy, the plethysmographic data indicate a supersensitivity of chronically denervated digital blood vessels to adrenaline injected intravenously. The increased responsiveness after chronic denervation was manifested by a greater shrinkage of the parts studied as well as by a prolongation of the response. A third manifestation of supersensitivity, a lowering of the threshold for the stimulus,[7] was not tested. This manifestation of increased sensitivity has been demonstrated for denervated lower extremities by Fatherree, Adson, and Allen[14] and for the vasodilator effect of small doses of adrenaline in striated muscle by Stein, Harpuder, and Byer.[32] The latter also demonstrated clear-cut increased vasoconstrictor responses to adrenaline in one of their 5 patients studied and "in the remaining cases, a more complete, but not impressive, response."

In experimental animals, the data demonstrate beyond reasonable doubt that smooth muscle is rendered supersensitive to chemical stimulation by sympathetic denervation (Cannon and Rosenblueth[7]). Specifically, there is abundant evidence that peripheral blood vessels become oversensitive in their responses to adrenaline after denervation.[11, 12, 18, 24, 26, 34] In man, agreement is less general, but the observations of most investigators do indicate that here, too, there is demonstrably increased sensitivity of blood vessels to adrenaline when denervated.[2, 8, 9, 10, 14, 17, 19, 25, 28, 30] Stein and associates[32] demonstrated supersensitivity of the vasodilator response of the blood vessels in leg muscles to small doses of adrenaline after sympathetic denervation. In fact, differences of opinion appear to be concerned less with whether or not sensitization by denervation actually occurs than they are with whether or not there is a real difference between the sensitizing effects of preganglionic and postganglionic denervations.

That such a difference of opinion should exist with regard to man is not surprising. In the first place, with few exceptions, most of the studies have used changes in the skin temperature as an index of vasoconstriction and vasodilatation in the skin. Except when a very steep gradient is maintained between the temperature of the body and that of the environment, changes in the blood flow are not reflected accurately by changes in the temperature of the skin.[16] Some of the many pitfalls encountered in the use of skin temperature to indicate changes in vasoconstrictor activity have been described by Fatherree and Allen.[13] In the studies presented here, the environmental temperature was controlled and maintained at 20° to 21° C. Vasomotor control in the nonsympathectomized patients or in those with recurrence was blocked by injecting the ulnar and median or the posterior tibial nerves with procaine. To be sure, the circulation of the acutely decentralized digit is not entirely comparable with

that of the chronically denervated digit (Fig. 2), but it is at least no longer subject to the great changes which the vasomotor centers can impose upon it. The greater circulation in the digit acutely decentralized by nerve block in contrast to the somewhat less active circulation in the chronically denervated finger would operate against the demonstration of supersensitivity in the latter. The demonstration of supersensitivity in the chronically denervated digit by absolute figures without resorting to percentiles is therefore of added significance.

It is important to point out, furthermore, that denervations of the upper extremity are not completely postganglionic even when the stellate ganglion is removed. At best, the majority of patients denervated by cervicothoracic ganglionectomy have had an only predominantly postganglionic denervation. On the other hand, the preganglionic types of denervation probably include a variable proportion of postganglionic fibers among those interrupted. It would

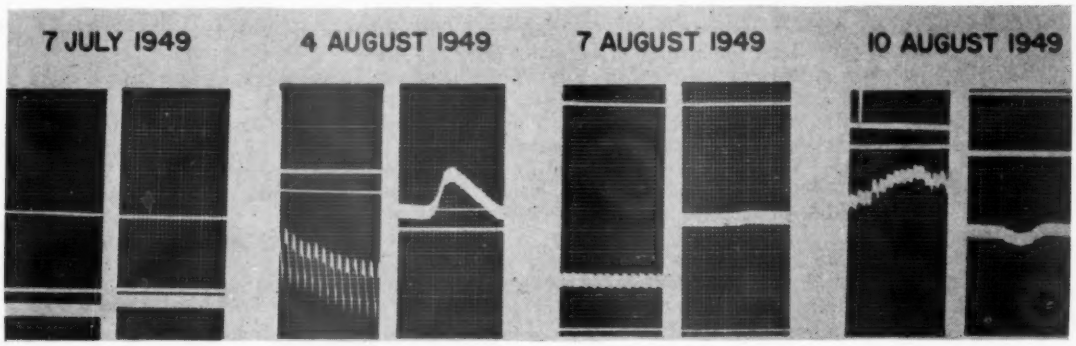

Fig. 2.—Records made by the Burch-Winsor plethysmograph on the left second toe of a patient with Raynaud's phenomenon preoperatively and on the second, fifth, and eighth days after left lumbar sympathetic ganglionectomy. These recordings were made after the patient had been in a constant temperature room at 20° C. for 1 hour. The first record on each day was one made with the slow photographic film speed and the second was a fast record.

be difficult, therefore, to demonstrate a possible greater sensitization after postganglionic denervation in such mixed material even if the 2 types of operation were done on opposite sides in the same patient.

The fact that a paresis is demonstrable in the cat for months after denervation[23] is no evidence that Cannon's "Law of Denervation"[6] does not operate under physiologic conditions. It must be recalled that chemical mediators, especially adrenine, are liberated into the circulation especially under conditions of emergency or stress. Except at such times or under experimental conditions when adrenaline is injected in small doses, "parodoxical" effects will not be apparent. As a matter of fact, the important feature for consideration is not whether or not supersensitivity of the blood vessels in man exists after sympathetic denervation but whether or not it plays an important role in the incidence of recurrence after sympathectomy for vasospastic conditions. Abundant evidence has accumulated that the phenomenon of oversensitivity of smooth muscle to humoral agents, while it does occur, is not primarily important as a cause of recurrence of vasospasm after sympathectomy. Simmons and Sheehan,[28] for example, found that while they could demonstrate increased

sensitivity of blood vessels early after denervation, the sensitivity decreased later as recurrence of symptoms took place. The decrease in oversensitivity is what one would expect if the recurrence was due to regeneration of vasomotor nerve fibers.[27] That return of nervous vasomotor activity is an important feature of recurrence of vasospasm after sympathectomy has been pointed out by several investigators.[3, 4, 15, 21, 29, 31] As Felder and co-workers[15] emphasized, surgical techniques should be directed toward methods for completeness of denervation and prevention of regeneration without concern for the phenomenon of increased sensitivity of blood vessels to humoral agents after sympathectomy.

REFERENCES

1. Ascroft, P. B.: The Basis of Treatment of Vasospastic States: An Experimental Analysis in Monkeys, Brit. J. Surg. **24**: 787-816, 1937.
2. Atlas, L. N.: Further Observations on the Etiology of Vasomotor Disturbances Following Peripheral Nerve Section, SURGERY **10**: 318-322, 1941.
3. Barcroft, H., and Hamilton, G. T. C.: Results of Sympathectomy of the Upper Limb, Lancet **1**: 441-448, 1948.
4. Barcroft, H., and Hamilton, G. T. C.: Further Observations on the Results of Sympathectomy of the Upper Limb, Lancet **2**: 770-771, 1948.
5. Burch, G. E.: A New Sensitive Portable Plethysmograph, Am. Heart J. **33**: 48-75, 1947.
6. Cannon, W. B.: A Law of Denervation, Am. J. M. Sc. **198**: 737-750, 1939.
7. Cannon, W. B., and Rosenblueth, A.: The Supersensitivity of Denervated Structures, New York, 1949, The Macmillan Company.
8. Daniélopolu, D., Aslan, A., and Marcou, I.: Le Tonus vasculaire du membre inferieur aprés la sympathectomie lombaire, étudié a l'aide de la réaction a l'adrenaline, Bull. Acad. de med., Paris **108**: 1488-1493, 1932.
9. Daniélopolu, D., Radovici, A., and Aslan, A.: Récherches sur la circulation péripherique chez l'homme, J. de physiol. et de path. gén. **24**: 27-37, 1926.
10. Doupe, J.: Studies in Denervation: Observations Concerning Adrenalin, J. Neurol. & Psychiat. **6**: 121-128, 1943.
11. Elliott, T. R.: The Action of Adrenalin, J. Physiol. **32**: 401-467, 1905.
12. Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Observations on the Hind Limbs of a Dog Ten Years Following Left Lumbar Sympathetic Ganglionectomy, Am. J. Physiol. **139**: 351-355, 1943.
13. Fatherree, T. J., and Allen, E. V.: The Influence of Epinephrine on the Digital Arterioles of Man; A Study of the Vasoconstrictor Effect, J. Clin. Investigation **17**: 109-118, 1938.
14. Fatherree, T. J., Adson, A. W., and Allen, E. V.: The Vasoconstrictor Action of Epinephrine on the Digital Arterioles of Man Before and After Sympathectomy, SURGERY **7**: 75-92, 1940.
15. Felder, D. A., Simeone, F. A., Linton, R. R., and Welch, C. E.: Evaluation of Sympathetic Neurectomy in Raynaud's Disease, SURGERY **26**: 1014-1031, 1949.
16. Fetcher, E. S., Hall, J. F., and Shaub, H. G.: The Skin Temperature of an Extremity as a Measure of its Blood Flow, Science **110**: 422-423, 1949.
17. Freeman, N. E., Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man, Am. J. Physiol. **107**: 529-534, 1934.
18. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, With Special Reference to the Effects of Denervation, Clin. Sc. **2**: 1-26, 1935.
19. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, Clin. Sc. **3**: 119-139, 1938.
20. Hampel, C. W.: Effect of Denervation on the Sensitivity to Adrenine of the Smooth Muscle in the Nictitating Membrane of the Cat, Am. J. Physiol. **111**: 611-621, 1935.
21. Haxton, H. A.: Regeneration After Sympathectomy and Its Effects on Raynaud's Disease, Brit. J. Surg. **35**: 69-76, 1947.
22. Heinbecker, P., and Bishop, G. H.: On the Mechanism of Spastic Vascular Disease, Proc. Soc. Biol. & Med. **32**: 152-154, 1934.
23. Kirgis, H. D., Reed, A. F., and Pearce, J. Y.: The Relative Effectiveness of Sympathetic Ganglionectomy and Section of Preganglionic Fibers in Inactivation of Smooth Muscle, SURGERY **28**: 941-949, 1950.
24. LeCompte, P. M.: Observations on the Return of Vascular Tone After Sympathectomy, Am. J. Physiol. **135**: 43-57, 1941.

25. Lewis, T., Harris, K. E., and Grant, R. T.: Observations Relating to the Influence of the Cutaneous Nerves on Various Reactions of the Cutaneous Vessels, Heart **14**: 1-15, 1929.

26. Meltzer, S. J., and Meltzer, C.: On the Effects of Subcutaneous Injection of the Extract of the Suprarenal Capsule Upon the Blood Vessels of the Rabbit's Ear, Am. J. Physiol. **9**: 252-261, 1903.

27. Simeone, F. A.: The Effect of the Regeneration of the Nerve Supply on the Sensitivity of the Denervated Nictitating Membrane to Adrenine, Am. J. Physiol. **120**: 466-474, 1937.

28. Simmons, H. T., and Sheehan, D.: The Causes of Relapse Following Sympathectomy of the Arm, Brit. J. Surg. **27**: 242-255, 1939.

29. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, Ann. Surg. **104**: 339-350, 1936.

30. Smithwick, R. H., Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity. An Additional Cause of Failure of Operations for Raynaud's Disease, Arch. Surg. **29**: 759-767, 1934.

31. Smithwick, R. H., Farmer, D. A., and Robertson, C. W.: To be published.

32. Stein, I. D., Harpuder, K., and Byer, J.: Reactivity of Blood Vessels in the Sympathectomized Human Leg, Am. J. Physiol. **158**: 319-325, 1949.

33. Telford, E. D.: The Technique of Sympathectomy, Brit. J. Surg. **23**: 448-450, 1935.

34. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Vasomotor Tonus of the Denervated Artery, Arch. Neurol. & Psychiat. **36**: 1251-1276, 1936.

DISCUSSION

DR. KEITH S. GRIMSON.—I find it is impossible to resist the temptation to enter into discussion of Dr. Simeone's excellent paper and debate with him the concept of "sensitization" of smooth muscle.

In a review of the literature 5 years ago, I came to the conclusion that the existence of some abnormal behavior or "sensitivity" had never been proved. Certainly it is agreed that denervated blood vessels react excessively to adrenaline or to cold, but is this sensitivity? It seems possible or probable that the exaggerated response is the normal response of a denervated blood vessel. In other words, when the central nervous system and the ganglia in the sympathetic nervous system are connected to a denervated smooth muscle and adrenaline is injected, then there is a peripheral response buffered by the central nervous control, a normal response of normally innervated smooth muscle. Only when all nerves are disconnected, as by an extensive sympathectomy, does one observe the normal peripheral action of the stimulus or the normal behavior of denervated smooth muscle. The increased response following preganglionic sympathectomy and the further exaggerated response following ganglionectomy are therefore normal rather than sensitization phenomena.

Dr. Simeone's excellent studies have clarified the definitely proved fact that pre- or postganglionic sympathectomy in patients is followed by increased reactivity to adrenaline and cold. A natural conclusion would be that sympathectomies of limbs are contraindicated. Though clinical results merit the continued use of sympathectomy of the legs, I have come to the conclusion that sympathectomies of the arms should be performed rarely, if ever, better results being obtained for conditions such as Raynaud's disease by continued use of adrenolytic or sympatholytic drugs.

Recent experiments performed with George Meyer, a medical student working in our laboratories, have demonstrated that the nictitating membrane of the cat, which has a moderately increased response to adrenaline following preganglionic sympathectomy, will exhibit an exaggerated response immediately after the injection of a ganglionic blocking agent, Etamon or SC-1950. The exaggerated response equals that with a control ganglionectomy on the opposite side. Interpretation requires consideration of isolated or decentralized sympathetic ganglia as nerve centers capable of a reflex buffering action and does not allow assumption that a "sensitization" occurs after 12 or 24 hours and when postganglionic nerve fibers degenerate.

DR. MICHAEL E. DEBAKEY.—Any discussion of this problem usually brings out certain controversial matters. I think that Dr. Simeone has greatly helped to clarify this problem. We have felt for a long time that there was a definite difference between the response of animals and of human beings to sympathectomy. About 12 years ago we tried to repeat in human beings the observations made on animals that there was a difference in the sensitivity response of denervated smooth muscle to circulating adrenaline. Dr. Burch and I, using this same plethysmograph, studied 2 patients with Raynaud's disease in whom a preganglionic sympathectomy had been done on one side and a ganglionic sympathectomy on the opposite side. We found that there was an apparent increased sensitivity on both sides. Over a period of time, however, it was our impression that actually there was a greater increase in sensitivity on the side in which the preganglionic sympathectomy had been done. It was also our distinct impression clinically that the patients had a greater degree of improvement on the side in which the ganglionic sympathectomy had been done. Our experience with ganglionic sympathectomies as compared with preganglionic sympathectomies in patients with Raynaud's disease leads me to believe that the long-term results are definitely better in patients having had ganglionic sympathectomy. For this reason, too, I am convinced that if the operation is of any value at all, it must be done in a manner to provide as thorough and complete denervation of the part as possible.

DR. F. A. SIMEONE (Closing).—I certainly appreciate the comments made by Dr. DeBakey and Dr. Grimson. Dr. Grimson's point is well taken, but with our present state of information on the subject, we cannot get very far with it. It comes down to a matter of definition, because if we want to call the chronically denervated structure as responding normally, we would then have to call the normally innervated one hyponormal and we are really back where we started from. As Dr. DeBakey has observed, the sensitivity of digital vessels decreases as time goes on. We demonstrated in animals, and Simmons and Sheehan showed in man, that this drop from supersensitivity is associated with recurrence of nerve activity.

CANCER OF THE TONGUE—A SURGICAL TECHNIQUE FOR A PRIMARY COMBINED EN BLOC RESECTION OF TONGUE, FLOOR OF MOUTH, AND CERVICAL LYMPHATICS

ARNOLD J. KREMEN, M.D.,* MINNEAPOLIS, MINN.

(From the Department of Surgery, University of Minnesota Medical School)

CANCER of the tongue causes in the area of 2 per cent of all cancer deaths and is the cause of more deaths than any other malignant growth of the head and neck.[12] Although reports of selected cases of early cancer of the tongue suggest that cure rates as high as 56 per cent may be obtained,[5, 12] most people reporting their over-all results note a 5-year survival rate of 14 to 28 per cent of cases.[1, 8, 14] In instances where demonstrable metastases have occurred to the cervical lymph nodes, cure rates are considerably less frequent, however, with Cade[5] reporting 9.2 per cent five-year survivals, Gibbel and associates[8] 4.6 per cent survivals, and the *Texas Cancer Bulletin,*[6] reporting a drop from 40 per cent 5-year survival to 10 per cent 5-year survival when lymph nodes are involved.

While there appears to be considerable variation of choice of therapy to the primary intraoral lesion, with opinions divided between radiation therapy, diathermy excision, conventional surgical excision, or combinations of these methods, most people concerned with the problem are in agreement that for management of cervical metastases, radical neck dissection presents the patient with his best opportunitiy for continued survival. However, heretofore, except in special circumstances, most plans of management have been discontinuous in the sense that therapy is first directed to the tongue, and only when it appears to be controlled is treatment directed to the cervical lymph nodes.

It is the purpose of this paper to present a surgical technique for management of most cases of cancer of the anterior two-thirds of the tongue which applies classical concepts of cancer surgery to this area, namely, en bloc removal of the primary lesion, intervening lymphatic channels, and regional lymph nodes. Such a plan can be effected in cancer of the tongue with good cosmetic and functional results and, in the twelve consecutive cases to be presented, with no operative mortality.

HISTORY

A number of illustrious pioneers of surgery, including Syme, Billroth, and Kocher, have concerned themselves with the problem presented by cancer of the tongue. Butlin[4] credited the first recorded attempt at extirpation of cancer of the tongue to Marchetti in 1664. Major, in 1827, divided the tongue down its central raphe and applied a ligature to the diseased half, and Jaeger,[9] in 1831, suggested splitting the cheek from the corner of the mouth to gain added exposure. Chaissaignac[7] in 1856 introduced the écraseur or tourniquet excision

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*Associate Professor of Surgery, University of Minnesota.

which, for a period, achieved considerable popularity, but was later abandoned. The submandibular approach to the tongue, first described by Regnoli[15] in 1838, was later modified by Billroth in 1874[2] and by Kocher[10] in 1880.

Division of the mandible in resecting cancer of the tongue was first carried out by Roux in 1836. Later Sedillot[19] (1844) proposed a similar technique, and Syme, in 1857 and later in 1865, divided the lip and symphysis of the mandible through an incision extending upward from the hyoid bone, and by this approach was able to excise most of the anterior portion of the tongue and floor of the mouth. Billroth[2] divided the jaw and soft parts at the side in two places, turned down a flap of skin and bone, and later replaced the bone by wiring. Trotter, in 1913,[21] reporting his large experience in the operative treatment of cancer of the mouth and pharynx, condemned the submandibular approach and in its place advocated an incision, the vertical portion of which extended through lip in the midline to beneath the jaw, then transversely below the mandible to the sternomastoid muscle. To gain exposure to the tongue he transected the mandible just in front of the insertion of the masseter muscle and in order to avoid infection he stressed the importance of placing the osseous transection as far away as possible from the soft tissue incision through the lower lip. After the glossectomy, the transected mandible was approximated with wires which usually had to be removed at a later time. He observed that although a considerable number of patients could be cured of their local disease, many succumbled later to gland involvement; he agreed with Butlin that treatment of the glands was as much a part of the plan of therapy as removal of the local growth. However, because of the real danger of infection in the planes of the neck at that time, Trotter did not feel that neck dissection should be a part of the primary operation but should be done at a later time. In the light of present experience with antibiotics, infection is no longer a compelling contraindication to such a combined resection, and it is therefore possible to plan and carry out a more complete en bloc removal of the site of primary growth, floor of the mouth, and glands of the neck as a one-stage procedure.

OPERATIVE PROCEDURE

As a preliminary procedure five to seven days before the formal operation, a tracheotomy and a Witzel type gastrostomy are performed upon all patients. The former provides an adequate airway during the operative procedure and, more important, assures a patent airway during the postoperative period. It is far better to anticipate this need than to have to provide it as an emergency measure postoperatively, after the patient has developed signs of respiratory obstruction with its added exhaustion, stress, and attendant anoxia. The gastrostomy is performed at the same time so that adequate nutrition can be maintained postoperatively while the oral cavity is healing and the patient is learning to swallow again. A gastrostomy tube for feeding purposes is tolerated with less distress by the patient than an indwelling nasogastric tube. Moreover, feedings given by gastrostomy, in our experience, are less likely to be regurgitated than similar feedings administered via a nasogastric tube.

The incision as shown in Fig. 1 begins over the medial end of the clavicle, extends obliquely upward over the anterior edge of the sternomastoid muscle to the mastoid process, then transversely beneath the mandible to the opposite submandibular area. A vertical extension is carried upward in the midline, bisecting the lower lip. After widely reflecting medial and lateral skin flaps to include the platysma muscle, the dissection is started at the lowermost portion of the neck, cutting the sternomastoid muscle from its sternoclavicular attachment and ligating and cutting the jugular vein at the level of the clavicle. The supra-

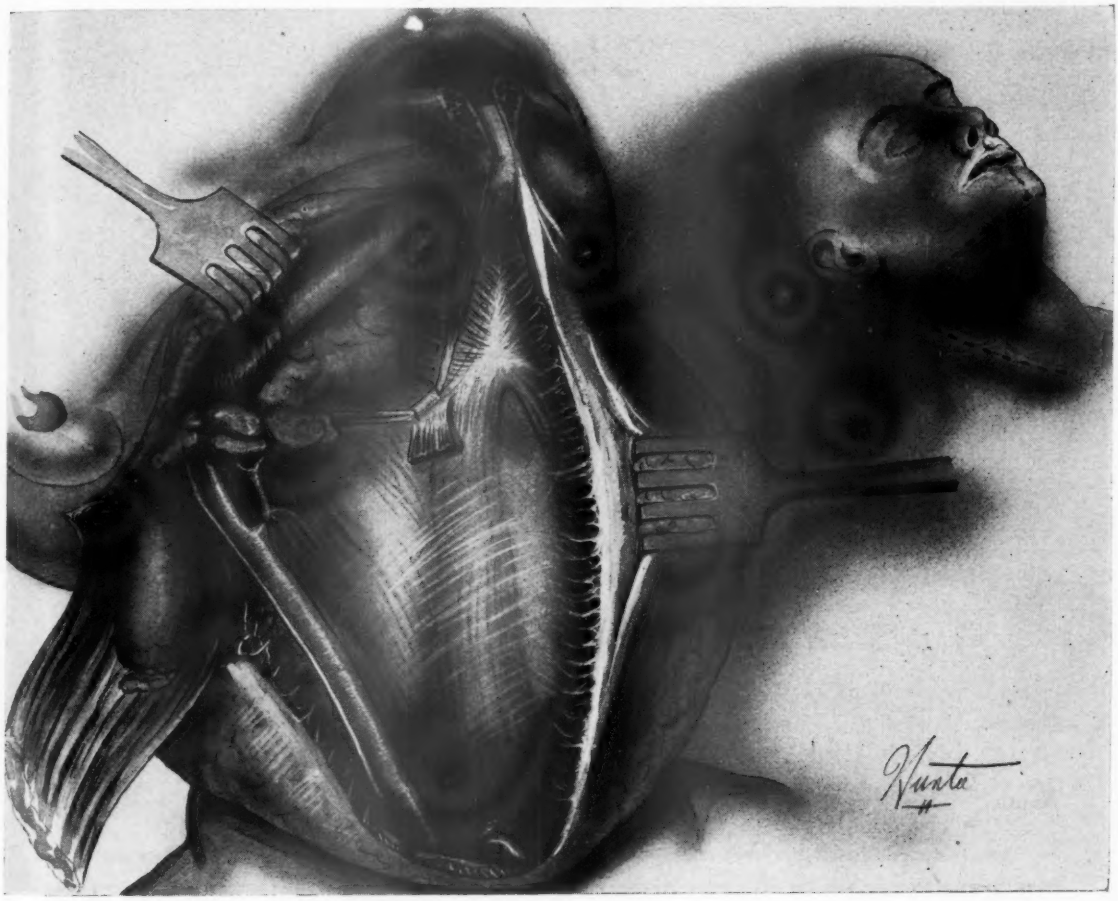

Fig. 1.—Inset in right upper corner shows the skin incision. The jugular vein and sternomastoid muscle have been cut in the lowermost portion of the neck and the radical neck dissection carried upward to the bifurcation of the carotid artery. The external carotid artery is ligated and the lip is vertically incised in the midline.

clavicular fossa is dissected free of its contents down to the prevertebral fascia, and the carotid artery is dissected from its sheath and adventitia, preserving the vagus nerve. The dissection is carried up to the bifurcation of the carotid artery, at which juncture the external carotid artery is ligated, a precaution that considerably reduces blood loss in the later phases of the operation. At this stage the operation is carried into the mouth (Fig. 2). The lower lip is transected in the midline, and the underlying mandible is cut with a Gigli saw in the same plane. The intraoral mucosal incision is then developed along the inner

aspect of the lower alveolar ridge back to the anterior pillar, or beyond, if necessary. In an edentulous patient, which many of these individuals are, this poses no problem. In the individual with good teeth, however, it is necessary to extract two or three of the incisor teeth to divide the mandible. In developing the mucosal incision in these patients it is necessary to preserve carefully a flap of five to six mm. of mucosa along the inner aspect of the alveolar ridge to which to suture residual mucosa in reconstructing the oral cavity.

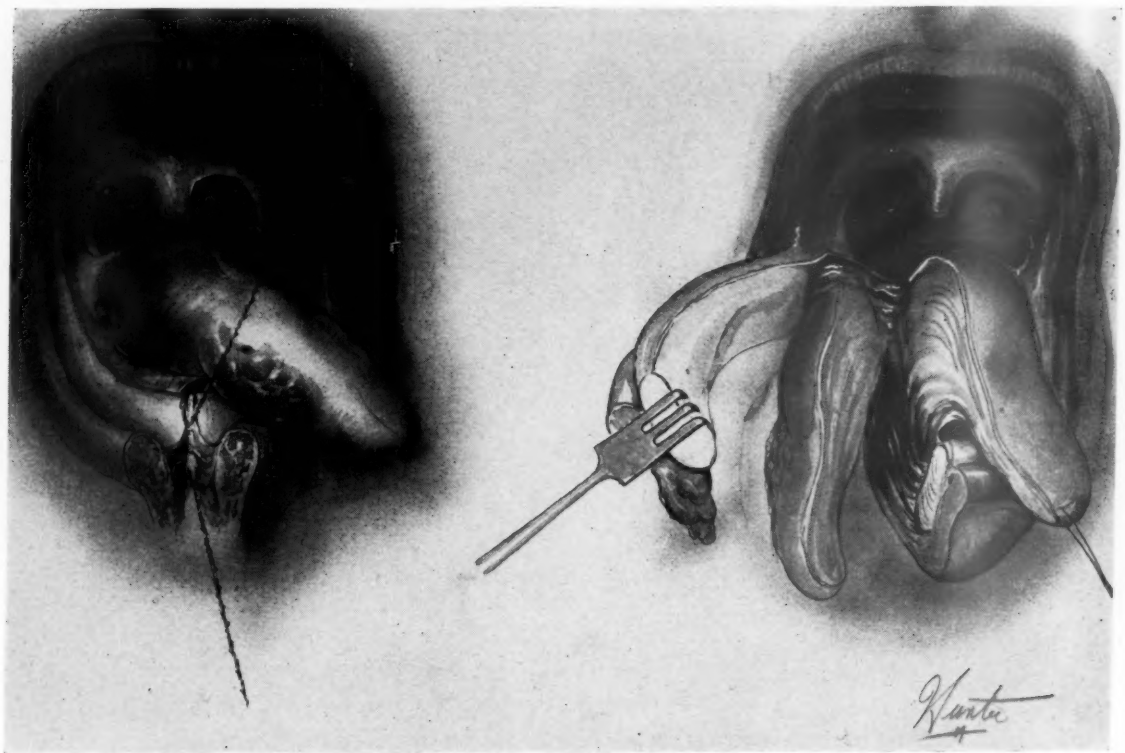

Fig. 2.—The illustration shows the transection of the mandible with a Gigli saw, the outline of the mucosal incision in the mouth, and the hemisection of the tongue and floor of the mouth.

After developing the mucosal plane along the alveolar ridge, the periosteum of the inner aspect of the mandible is stripped away along with the attachments of the genioglossus, hyoglossus, and digastric muscles. This allows the mandible to be retracted laterally, providing excellent exposure to the tongue, mouth, and pharynx. The tongue is then divided down the midline as far posteriorly as necessary. In several instances this has been carried back to the level of the epiglottis. The incision is then curved lateralward to connect with the alveolar ridge incision, including the tonsillar pillar and portions of the soft palate, if indicated. This specimen of mucosa, tongue, and floor of mouth is then dissected downward, removing all of the contents and muscles of the submaxillary triangle to the previously made neck dissection area (Fig. 3). The upper portion of the cervical neck dissection is then completed by ligating the jugular vein at the level of the styloid process, cutting the sternomastoid muscle from its mastoid

attachment, sacrificing the external carotid artery, and taking the digastric and stylohyoid muscles, thus delivering the entire specimen. In addition, a contralateral conventional submaxillary gland dissection is performed.

Reconstruction of the oral cavity (Fig. 4) is accomplished by mobilizing the residual tongue and suturing the cut edge of its dorsal mucosa to the alveolar ridge until the midline is approached, and then bringing mucosa from the under

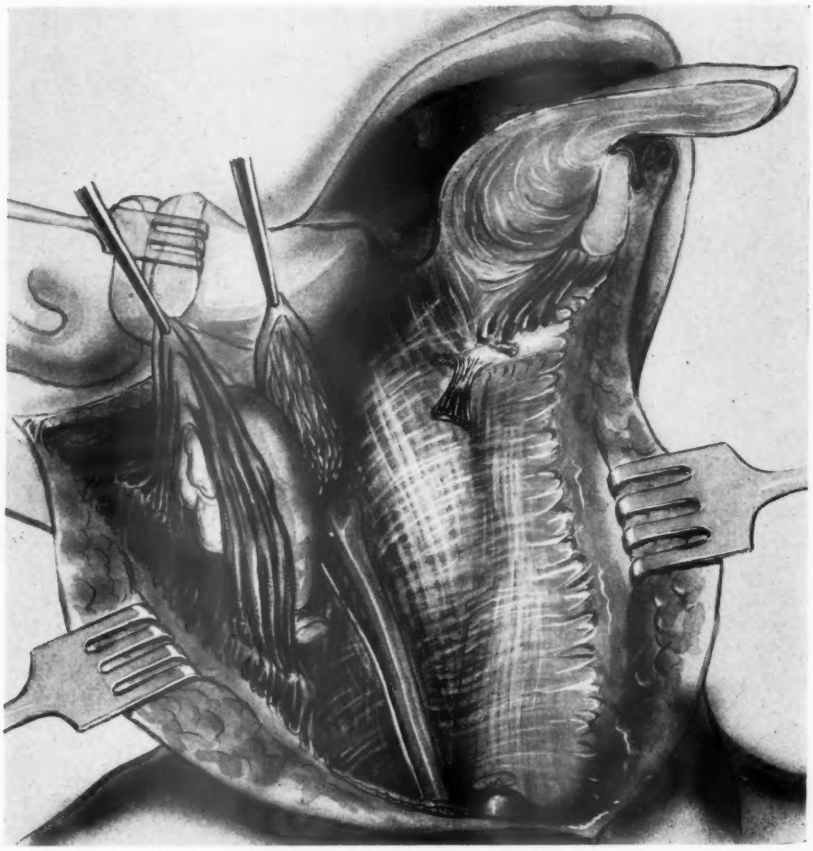

Fig. 3.—The illustration shows the completion of the intraoral and submaxillary dissection with resected segment of tongue and floor of mouth dissected down to join the neck dissection. The digastric muscle is sacrificed along with the hypoglossal nerve, the external carotid artery, and the entire upper deep cervical glands. The upper end of the neck dissection is then completed in the usual fashion.

surface of the tongue and residual floor of the mouth to approximate this area. The mandible is brought back into its normal position and fixed with two stainless steel wires placed through drill holes, following which the lip is sutured and the flaps of the neck dissection are similarly closed. Penrose drains brought out through stab wounds posteriorly are left in the submaxillary and supraclavicular areas.

POSTOPERATIVE COURSE

All oral feedings are withheld for a week postoperatively, after which time the patient gradually learns to eat again. At first some patients have ex-

perienced difficulty in swallowing and will exhibit a tendency to aspirate material into the trachea. However, usually by two to four weeks they are able to take all nourishment by mouth, and gastrostomy feedings can be discontinued. During the period of readjustment fluoroscopic observation with radiopaque material has shown a tendency for material to pool in the pyriform sinuses and at times to spill over into the larynx. In one instance the presence of the open tracheot-

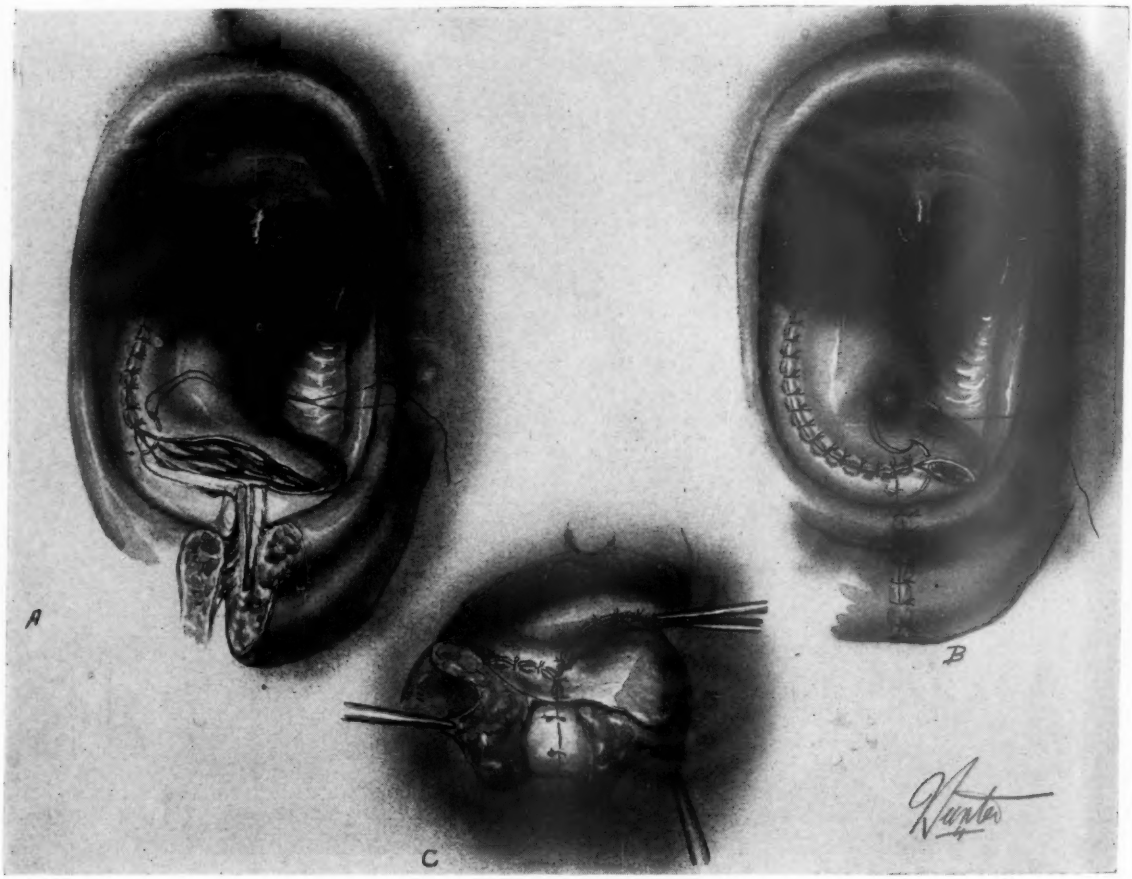

Fig. 4.—*A*, This shows the reconstruction of the oral cavity. The dorsal mucosal edge of the tongue is sutured to the mucosa along the alveolar ridge after swinging the mandible back to normal position. *B*, Anteriorly the under side of the tongue and mucosa of residual floor of the mouth is approximated to complete the reconstruction of the oral cavity. The mucosa of the raw edge of the short remaining anterior tip of the tongue is approximated and the lip sutured in its normal position. *C*, Two stainless steel wires approximating the severed mandible.

omy tube appeared to potentiate this difficulty in deglutition. With the tube in place and open, material was observed to spill into the larynx on swallowing, and after plugging and removing the tracheotomy tube this no longer occurred.

Although the findings in this one instance were quite striking, this has not been a constant observation. It does suggest, however, that in certain individuals the presence of a tracheotomy tube may alter the mechanics of deglutition to prevent proper elevation of the larynx on swallowing so that spilling over can occur. However, until more definite data are obtained on this point, it is felt

that the tracheotomy should be maintained so that if aspiration occurs from other causes, tracheal toilet can easily be carried out. After a period of readjustment, however, all patients have learned to swallow without difficulty.

The mechanics of talking, similarly, have to be readjusted. By two weeks these patients can make their wishes understood adequately, and after six to eight weeks they can converse without difficulty, although there may remain a mild defect in articulation. The mandible has regularly healed without difficulty, restoring the facial contour to normal, and in no instance has it been necessary to remove the wires approximating the severed mandible.

DISCUSSION

In the surgical management of cancer of the tongue, as in other areas, curative treatment requires consideration of the regional lymphatic spread as well as the site of origin, providing, of course, that the primary site offers promise of being controlled. In the literature varying opinions have been expressed concerning the validity of carrying out extensive surgical procedures to lymphatic bearing areas in the neck if they do not appear to be clinically involved with cancer. Although Martin and associates[12] have stated that over 60 per cent of unselected cases of cancer of the tongue metastasize at some time during the course of the disease, they also observed that in a highly selected group of 118 patients who did not have demonstrable metastases at the time of treatment and in whom the primary lesion remained permanently controlled, only 22 per cent later demonstrated cervical metastases. However, since these patients were selected for the crucial item of remaining free of disease, it is possible that these lesions were less active biologically than in the average case of cancer of the tongue. Roux-Berger,[17] in the Curie Foundation of Paris, on the other hand, has routinely carried out radical neck dissections after treating the primary lesion in the tongue by radiation. Reviewing his material in 1949 he found 81 of 173 patients (46 per cent) to have pathologically involved lymph nodes when the operation was carried out prophylactically for clinically nonpalpable nodes. Equally important is the five-year cure rate of 27 per cent in the group of pathologically positive, clinically negative cases compared to the five-year cures of 11 per cent in the clinically positive, pathologically positive group of cases. This suggests that, contrary to the situation in cancer of the lip, where the salvage rate is approximately the same for microscopically involved lymph nodes in the "prophylactic" or "therapeutic" groups of cases,[13] in cancer of the tongue those patients with involved lymph nodes do better if these metastases are properly removed before they became large enough to become clinically apparent. The high yield (46 per cent) of pathologically involved nodes and the improved salvage of these cases would strongly support the thesis that removal of regional lymphatic-bearing tissue should be an essential part of the management of operable cases of cancer of the tongue. If such a plan can be effected by an incontinuity operation, this thesis can be more strongly supported. In the relatively small series reported here, four of nine cases (44 per cent) exhibited microscopic evidence of lymph node metastases which were not evident on clinical examination. Morever, this is a base line figure, for since this material

TABLE I. SUMMARY OF PATIENTS OPERATED UPON

NAME	AGE (YEARS)	LESION	ONSET OF SYMPTOMS	OPERATION	LYMPH NODES	POSTOPERATIVE COURSE
1. Mrs. K. G. (U. H. 790285)	62	5 × 3 cm. squamous-cell carcinoma of left tongue anterior to pillar, extending to floor of mouth	Dec. 1947	July 23, 1948, combined left hemiglossectomy, resection of floor of mouth and left radical neck dissection	Clin. 0 Path. +	Developed orocutaneous fistula which closed spontaneously; free of disease Jan. 25, 1951
2. Mrs. E. E. (U. H. 799894)	68	3 × 2 cm. squamous-cell carcinoma left anterior 2/3 of tongue starting at the tonsillar pillar and involving under side of tongue and floor of mouth on left	Dec. 1948	Feb. 21, 1949, combined left hemiglossectomy, resection of floor of mouth and left radical neck dissection	Clin. 0 Path. +	Developed + node in right deep upper cervical area; right radical neck dissection Sept. 1, 1950, free of demonstrable disease Jan. 4, 1951
3. Mr. B. F. (U. H. 803118)	67	4 × 3 cm. squamous-cell carcinoma left anterior 2/3 of tongue involving floor of mouth on left	July 1948	May 3, 1949, combined left hemiglossectomy, resection of floor of mouth and left radical neck dissection with right suprahyoid dissection	Clin. + Path. + Multiple involved nodes completely replaced by tumor	Developed temporary fistula which closed in 6 weeks; local lesion controlled until death. Recurrence in left neck Dec. 1949; x-ray treatment; died March, 1950
4. Mr. C. M. (U. H. 802945)	35	4 × 2 cm. squamous-cell carcinoma of anterior 2/3 of right side of tongue	Jan. 1949	April 19, 1950, combined right hemiglossectomy, resection of floor of mouth and radical right neck dissection	Clin. 0 Path. +	Small fistula which closed spontaneously; recurrence in neck Oct. 1949; x-ray treatment; died March 6, 1950
5. Mr. E. L. (Va Hosp. 90,-989)	53	2 cm. squamous-cell carcinoma of anterior 2/3 left side of tongue involving under surface and floor of mouth; palpable right submaxillary lymph gland	Apr. 1949	May 26, 1949, combined left hemiglossectomy, resection of floor of mouth, radical left neck dissection, and right suprahyoid neck dissection	Clin. + Path. 0	Free of disease Sept. 1950
6. Mrs. M. P. (U. H. 807167)	63	Squamous-cell carcinoma right tongue treated with x-ray and radon implantation Aug. 1949; persistence in tongue and involved right submaxillary and deep cervical lymph nodes Nov. 1949	Mar. 1949	Dec. 12, 1949, combined right hemiglossectomy, resection of floor of mouth, right radical neck dissection, and left suprahyoid dissection	Clin. + Path. +	Free of disease Dec. 14, 1950

7. Mrs. O. B. (U. H. 813740)	69	Squamous-cell carcinoma right lateral aspect of tongue; excision biopsy Dec. 23, 1949	Nov. 1949	Jan. 27, 1950, combined right hemiglossectomy, resection of floor of mouth, right radical neck dissection, and left suprahyoid dissection	Clin. 0 Path. 0	Free of disease Sept. 7, 1950
8. Mr. O. H. (U. H. 819207)	68	Squamous-cell carcinoma right lateral aspect of tongue with involvement of anterior tonsillar pillar, 2.5 × 1.5 cm. diameter, preoperative x-ray treatment	May 1, 1950	June 9, 1950, combined right hemiglossectomy, resection of right tonsillar pillar and portion of right soft palate; resection of floor of mouth, right radical neck dissection, and left suprahyoid dissection	Clin. 0 Path. 0	Well Dec. 24, 1950
9. Mr. W. F. (U. H. 819781)	78	Squamous-cell carcinoma left lateral aspect of tongue involving anterior tonsillar pillar and extending posteriorly to the pillar; lesion 3 × 2 cm. diameter	May 1950	June 27, 1950, combined left hemiglossectomy, resection of left floor of mouth, left radical neck dissection, and left suprahyoid dissection	Clin. 0 Path. 0	Well Jan. 17, 1951
10. Mr. A. J. (U. H. 824164)	44	Squamous-cell carcinoma of left tongue and floor of mouth 3 × 3 cm. diameter	Sept. 1, 1950	Oct. 17, 1950, combined left hemiglossectomy, resection of floor of mouth, left radical neck dissection, and right suprahyoid dissection	Clin. 0 Path. 0	Well Jan. 8, 1951
11. Mr. J. K. (U. H. 825709)	47	Squamous-cell carcinoma of left anterior tongue and floor of mouth; lesion 2 × 3 cm. diameter	July 1950	Dec. 19, 1950, combined left hemiglossectomy, resection of floor of mouth, left radical neck dissection, and right suprahyoid dissection	Clin. 0 Path. +	Well healed Jan. 11, 1951
12. Mrs. E. E. (U. H. 826738)	63	Squamous-cell carcinoma of right anterior tongue; lesion 1½ × 1 cm. diameter	Oct. 10, 1950	Dec. 26, 1950, combined right hemiglossectomy, resection of floor of mouth, right radical neck dissection, and left suprahyoid dissection	Clin. 0 Path. 0	Well healed, no complaints Jan. 19, 1951

was not serially sectioned, but only sampled at random, it is possible that additional cases may have had metastases which were not found by the pathologist. Saphir and Amromin[18] reported serial section studies in thirty patients whose

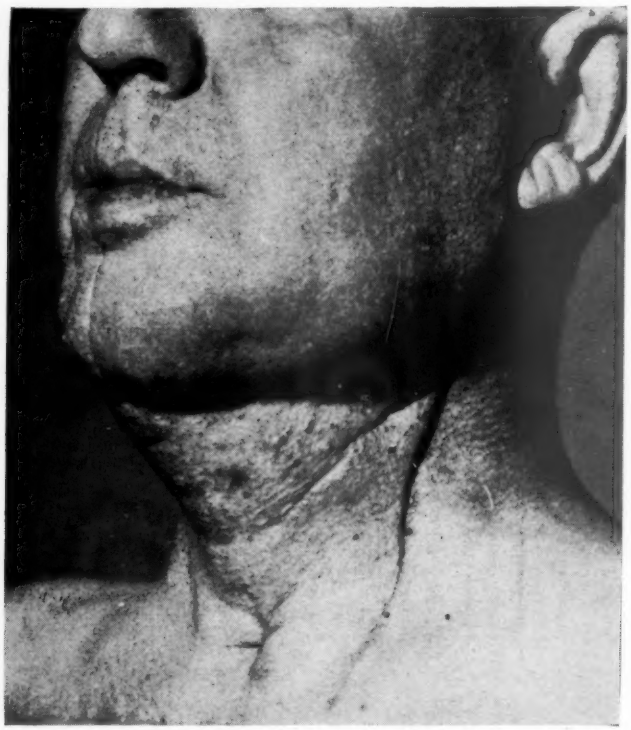

Fig. 5 (Case 5).—The appearance of E. L. 1 month after surgery.

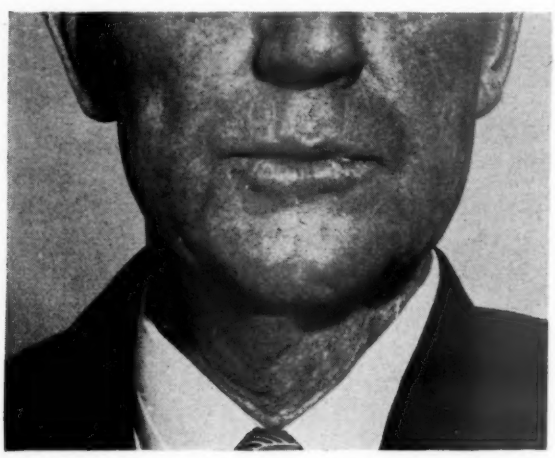

Fig. 6 (Case 5).—The appearance of E. L. 10 months after surgery.

axillary lymph nodes were removed by radical mastectomy and reported as negative by routine pathologic examination. Of these, ten cases, or 33 per cent, were demonstrated to contain cancer cells by serial section examination.

In all, twelve patients have been operated upon in the fashion described. There have been no operative deaths in the group, but two of the twelve patients (Cases 3 and 4) subsequently succumbed from recurrent cancer in the neck

Fig. 7.

Fig. 8.

Figs. 7 and 8 (Case 6).—The appearance of M. P. 6 months postoperatively.

without local recurrence ten and eleven months after their operations. Both had extensive primary lesions and involved lymph nodes, although C. M. (Case 4) did not have palpable glands prior to operation. One patient, E. E. (Case 2), who was operated upon Feb. 21, 1949, was found to have involved lymph glands

which were not apparent preoperatively. Subsequently she developed clinical metastases in the deep upper cervical glands on the contralateral side without local recurrence in the residual tongue. On Sept. 1, 1950, eighteen months after the original operation, she had another radical neck dissection performed for this contralateral spread and to date she has remained well. All of the other patients are at present free of demonstrable disease, although in 5 it has been less than a year since operation.

With the mandible divided as described previously, excellent exposure has been gained for the intraoral phase of the operation, and the plan of carrying out an en bloc resection has been greatly facilitated. No untoward complications have resulted from this maneuver. All have healed postoperatively, with the mandibular arch and the facial contour preserved. Figs. 5, 6, 7, and 8 show the final appearance of two of these patients (Cases 5 and 6 of Table I).

If one is suspicious of the mandible being invaded by tumor it should unhesitatingly be sacrificed. However, in most instances of cancer of the tongue this occurs only in the far-advanced cases, and in the majority of cases the advantages that a mandibular resection provides in terms of exposure can be gained by this technique without permanent sacrifice of the structure.

CONCLUSIONS

A technique is described for surgical management of cancer of the tongue which provides for an en bloc resection of the cancer in the tongue, floor of the mouth, and cervical lymphatic drainage area. Such a plan can be effected with functional and cosmetic results that are acceptable to most patients.

REFERENCES

1. Berven, Elis: End Results of Treatment of Cancer of the Tongue, Am. J. Roentgenol. 63: 712, 1950.
2. Billroth, T.: Langenback's Archiv. Bd. 16: Hft. 2, 1874.
3. Billroth, T.: Arch. f. klin. Chir. p. 681, 1862.
4. Butlin, H. T.: Diseases of the Tongue, Philadelphia, 1885, Lea Brothers, pp. 303-332.
5. Cade, Sir Stafford: Treatment of Cancer of the Tongue, Am. J. Roentgenol. 63: 716, 1950.
6. Cancer of the Tongue, Texas Cancer Bull. 1: 15, 1948.
7. Chaissaignac: Traite de l'ecrasement lineaire, Paris, 1856.
8. Gibbel, M. L., Cross, J. H., and Ariel, I. M.: Cancer of the Tongue, Cancer 2: 411, 1949.
9. Jaeger: De Extirpatione Erlangen, 1832.
10. Kocher: Deutsche Ztschr. f. Chir. 13: 146, 1880.
11. Martin, H. E.: History of Lingual Cancer, Am. J. Surg. 48: 703, 1940.
12. Martin, H. E., Munster, H., and Sugarbaker, E. D.: Cancer of the Tongue, Arch. Surg. 41: 888, 1940.
13. Modlin, J.: Neck Dissections in Cancer of the Lip, SURGERY 28: 404, 1950.
14. Peterson, D., and Stenstrom, K. W.: Carcinoma of the Tongue, Staff Bull. U. of Minn. Hosp. 14: 15, 1948.
15. Regnoli: Nuovo metado per l'estirpazione della lingua, Pisa, 1838; Schmidt's Jahr. 24: 214, 1839.
16. Roux: Quoted by Butlin.[4]
17. Roux-Berger, J. L., Baud, M., and Courtial, J.: Cancer de la partie mobile de la langue. Le curage ganglionaire prophylactique est-il justifie? Statistique de la Foundation Curie, Mém. Acad. de chir. 75: 120, 1949.
18. Saphir, O., and Amromin, G. D.: Obscure Axillary Lymph Node Metastases in Carcinoma of the Breast, Cancer 1: 238, 1948.
19. Sedillot: Gaz. d. hôp. p. 83, 1844.
20. Syme, J.: Excision of the Tongue, Lancet 1: 115, 1865.
21. Trotter, W.: Principles and Technique of the Operative Treatment of Malignant Disease of the Mouth and Pharynx, Lancet 1: 1075-1081, 1147-1152, 1913.

DISCUSSION

DR. DANELY P. SLAUGHTER.—I think this was an excellent presentation and a very worth-while clinical research in attempting to save the mandible in these advanced carcinomas of the tongue. The exposure certainly is excellent. However, I should like to caution about applying minimal or temporizing measures to these lesions.

We have been attempting to do a similar procedure to save the mandible by a type of operation that is a little bit different from this. We call it a "pull-through," after Grant Ward's terminology. I believe he credits Mark Ravitch in having done the first one; however, our procedure is done in reverse. We have been doing a radical neck dissection up to the mandible and then cutting into the floor of the mouth from below subperiosteally. It is then possible to pull the tongue down into the neck and do the same type of procedure that he has done in continuity, and it can be done either to the anterior or posterior third. We have taken out the base of the tongue through this exposure without sectioning the mandible at all. It is a feasible procedure and repair, and although it is more difficult, more awkward I should say, than with the mandible swung back, it is possible. We have done about six such cases with primary healing and with no infection in any of them. However, it is going to be like the problem of a laryngo-fissure, the indications for which have been too often overextended to save the larynx. We must not let sentimental regard for the mandible get in the way of curing cancer. I have already had a couple of recurrences in these cases, and in that type we should have taken the jaw and not tried to salvage it. So I think the indications for a minimal procedure must be very carefully evaluated. As to the problem of incidence of involved nodes in the neck when they are not clinically evident, our figures run 10 per cent in the group in which we have done a neck dissection in continuity with or without taking the mandible when there was no clinical evidence of disease.

DR. JOHN J. MODLIN.—Dr. Kremen is to be congratulated on this discussion of the technique of jaw-neck dissection. I agree with Dr. Slaughter concering preservation of the mandible, however, since we have not been able to preserve the mandible safely in the majority of patients in which this operation has been done. At the Ellis Fischel Cancer Hospital, a total of eighty-three jaw-neck dissections have been done, relatively few, however, for carcinoma of the tongue. The majority of operations were performed for lesions of the buccal mucosa, lower gingiva, and for metastases from cancer of the lip which have invaded the mandible. These patients have been closely followed and, in our experience, loss of a portion of the mandible has been compatible with a happy existence. These patients have been able to swallow and to talk without great difficulty and the esthetic result is often surprisingly good. It is too early to talk in terms of cure rates following jaw-neck dissection for intraoral cancer. However, preliminary results are encouraging. In the group of eighty-three operations performed at the Ellis Fischel Cancer Hospital, twenty-nine were performed prior to five years ago. Of these, fourteen patients are alive and apparently free of disease. In regard to tracheostomy, we also perform this routinely in all jaw-neck dissections in order to provide an adequate airway in the early postoperative period. However, we have not believed that staging of this procedure is necessary, the tracheostomy being done at the conclusion of the operation.

DR. HENRY ROYSTER.—I would like to point out that when the decision is made to save the mandible it must be realized that the tissues just beneath the mandible and external to it are actually attached to the periosteum. The deep cervical fascia comes up from the neck and becomes one with the periosteum around the mandible. The skin and subcutaneous tissue send septa down through that deep fascia and when lymph nodes in that region become enlarged they become fixed to the mandible. Since we do not know in any given case where nodes are not palpable which ones are going to contain cancer, and the ones from the tongue might easily go first to the submaxillary nodes, I think one would be taking a chance in not removing the mandible. We are interested in saving the patient's life and I certainly agree that the removal of the mandible is very little hazard to the patient's functioning in after years, either in so far as appearance is concerned, or in eating, swallowing, or talking.

DR. ARNOLD J. KREMEN (Closing).—I want to thank Dr. Slaughter, Dr. Modlin, and Dr. Royster for discussing the paper. It was not my purpose to attempt to suggest that the mandible must always be salvaged. If there is any suggestion that the mandible is either possibly or remotely possibly involved by cancer, I also feel that it should be sacrificed. However, in most cases of cancer of the tongue the involvement over toward the mandible is a late result and in the majority of cases of cancer of the tongue, in the garden variety of cases of cancer of the tongue, aside from late cases, I do not believe it is necessary to sacrifice the mandible. Although patients get along without portions of the mandible, I see no reason why they should be deprived of it routinely. In most cases of cancer of the tongue usually the inner side of the alveolar ridge is free. Also, although they may involve the floor of the mouth, many cases are still a considerable distance away from the mandible. It has been suggested by Dr. Ward that some of the lymphatics draining the tongue go through the periosteum along the inner segment of the mandible. Certainly that is a potential channel, but by sacrificing the periosteum along the inner side of the mandible, which peels away very readily, it is possible, I believe, that this potential channel of lymph drainage can be controlled. In the twelve patients that we have had, although two have subseqently died of recurrences in the neck, we have not yet seen a local recurrence in the oral cavity.

THE RENAL AND HEPATIC BLOOD FLOW, GLOMERULAR FILTRATION RATE, AND URINARY OUTPUT OF ELECTROLYTES DURING CYCLOPROPANE, ETHER, AND THIOPENTAL ANESTHESIA, OPERATION, AND THE IMMEDIATE POSTOPERATIVE PERIOD

D. V. Habif, M.D., E. M. Papper, M.D., H. F. Fitzpatrick, M.D., P. Lowrance, M.D.,* C. McC. Smythe, M.D.,** and S. E. Bradley, M.D., New York, N. Y.

(From the Departments of Surgery and Medicine, Columbia University College of Physicians and Surgeons, and the Surgical, Anesthesiology, and Medical Services of the Presbyterian Hospital)

RENAL functional disturbances occur commonly in patients during and after general anesthesia and operation. It has been shown clearly that urine formation is diminished in association with a reduction in glomerular filtration and renal blood flow during the action of cyclopropane, ether, and certain barbiturates.[1-5] Oliguria with retention of water and salt may be observed postoperatively. These phenomena may be attributed, in part at least, to acute and persistent derangements in the distribution, volume, and composition of body fluids.[6, 7] Such changes may affect the kidney directly or indirectly by provoking unusual neural and humoral activity. Moreover, it is probable that widespread cardiovascular adjustments occur in response to the need to maintain the arterial pressure, the cardiac output, and the perfusion of vulnerable tissues under the stress of anesthesia and operative procedures.[8, 9] To what extent this homeostatic circulatory reaction, in which the kidney participates, may be implicated and to what extent the noxious action of anesthetic drugs or operative trauma and pain must be blamed remains unsettled. Since the exact character of the changes in discrete renal functions is still uncertain, a study of glomerular filtration and urinary excretion of water and electrolytes was made in normal human subjects during anesthesia, operation, and the immediate postoperative period. Renal and hepatic blood flow were measured in order to evaluate the relationship between systemic vascular adjustments and the defect in urine formation.

METHODS

The subjects of this study were thirty-four patients admitted to The Presbyterian Hospital for various major surgical procedures. For the most part, they were young adults in excellent health, without evidence of renal or cardiovascular disease. Two had hypertensive disease without significant cardiac involvement and one had edema of unknown origin.

Each subject was examined in the resting, fasting state about one hour after awakening in the morning. In nine no narcotic premedication was given, but the remainder received meperidine (50 to 100 mg.). Atropine (0.5 mg.) or scopolamine (0.5 mg.) was administered to all subjects at least 1 hour prior

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*Markle Scholar in Medical Research.

**American College of Physicians Fellow in Medicine.

TABLE I. EFFECT OF

PATIENT	AGE (YEARS)	DIAGNOSIS	PROCEDURE	BP (MM. HG)	GFR (ML. PER MINUTE)	ERPF (ML. PER MINUTE)	FF (PER CENT)	V (ML. PER MINUTE)
W. G.	39	Fistula in ano	Control	108/68	131	584	22	10.0
			meperidine	98/60	147	446	33	2.7
C. B.	43	Edema of legs (cause undetermined)	Control	110/64	57	460	12	8.4
			meperidine	—	45	309	15	2.2
K. A.	46	Peptic ulcer	Control	124/76	80	466	17	5.9
			meperidine	102/68	61	257	24	0.4
M. V.	52	Rheumatoid arthritis	Control	140/84	60	329	18	7.3
			meperidine	120/84	35	188	19	0.7
P. B.	25	Rheumatoid arthritis	Control	112/64	91	490	18	1.2
			meperidine	110/60	75	471	16	0.4
A. S.	24	Inguinal hernia	Control	110/60	108	509	20	7.4
			meperidine	100/60	131	550	24	4.2
A. W.	49	Inguinal hernia	Control	104/74	118	616	19	1.2
			meperidine	108/64	69	348	20	0.3
A. Wa.	39	Inguinal hernia	Control	100/66	137	702	19	3.0
			meperidine	110/70	75	354	21	0.9

*All control figures are averages of 2 or more urine collection periods, each 10 minutes or longer. The values during anesthesia and operation are single periods showing the maximal change. The recovery period is always that period immediately following termination of anesthesia, usually lasting from 10 to 20 minutes. Abbreviations are as follows: BP, arterial pressure (sphygmomanometer); GFR, glomerular filtration rate (inulin clearance); ERPF, effective renal plasma flow (para-aminohippurate clearance); FF, filtration fraction (GFR/ERPF); V, urine flow; U_{Na}, U_K, and U_{Cl}, urinary concentration of sodium, potassium, and chloride ions, respectively; $U_{Na}V$, U_KV, $U_{Cl}V$, urinary excretion of sodium, potassium, and chloride ions; $U_{Na}V/GFR$., and so on, urinary excretion of sodium, potassium, and chloride ions relative to glomerular filtration. Meperidine (100 mg. in all except A. S., who received 50 mg.) was given subcutaneously.

to study. No effort was made to promote water diuresis. The glomerular filtration rate was measured by the inulin clearance, effective renal plasma flow by the sodium para-aminohippurate* (PAH) clearance, and estimated hepatic blood flow (EHBF) by the bromsulfalein (BSP) method. At the outset, the bladder was emptied by manual expression after catheterization and all urine secreted during an accurately timed period of approximately ten minutes was collected and saved as a "blank." An intravenous infusion of inulin, PAH, and/or BSP was appropriately made up in glucose (5 per cent in distilled water) and in a few instances in 0.85 per cent sodium chloride solution to maintain the plasma concentration of inulin close to 20 mg. per cent, of PAH at 2 mg. per cent, and of BSP at 1 mg. per cent. These levels were reached quickly by the injection of small "priming" doses of PAH 3 mg., inulin 3 Gm., and BSP 150 mg. The infusion was administered intravenously at a regular rate of approximately 4 ml. per minute, controlled by a calibrated Murphy drip and tunnel clamp.

After a thirty-minute period of equilibration, the bladder was emptied and the urine collected and discarded. Blood was taken from a vein in the opposite arm at this time and thereafter at intervals of forty-five to sixty minutes. All urine was collected quantitatively at ten- to sixty-minute intervals, depending on the rate of urine flow, and the bladder washed out with sterile, distilled water in order to assure complete emptying. When measurements of BSP clearances and estimated hepatic blood flow were to be made, a venous

*We are indebted to Dr. W. Boger and the Medical Research Division of Sharp and Dohme, Inc., Philadelphia, Pa., for a generous supply of sodium para-aminohippurate.

MEPERIDINE ON RENAL FUNCTION*

U_{Na} (MEQ. PER LITER)	U_K (MEQ. PER LITER)	U_{Cl} (MEQ. PER LITER)	$U_{Na}V$ (μEQ. PER MINUTE)	U_KV (μEQ. PER MINUTE)	$U_{Cl}V$ (μEQ. PER MINUTE)	$U_{Na}V/GFR$ (μEQ. PER ML.)	U_KV/GFR (μEQ. PER ML.)	$U_{Cl}V/GFR$ (μEQ. PER ML.)
61.7	4.1	56.0	602.0	41.3	47.0	4.5	0.3	4.1
67.8	15.8	68.9	183.3	42.8	186.0	1.8	0.3	1.3
19.3	2.0	–	161.7	16.3	–	2.8	0.3	–
32.8	5.2	–	73.4	11.7	–	1.6	0.3	–
10.8	9.6	–	65.2	58.0	–	0.8	0.7	–
46.0	85.2	–	16.2	30.0	–	0.3	0.5	–
23.6	1.5	–	171.0	11.1	–	2.9	0.2	–
97.3	8.2	–	66.6	5.6	–	1.9	0.2	–
48.2	19.0	–	60.1	23.5	–	0.7	0.3	–
118.5	69.0	–	43.1	25.1	–	0.6	0.3	–
43.9	5.3	49.8	328.2	39.2	367.8	3.0	0.4	3.3
44.2	14.2	52.8	186.8	59.9	223.0	1.4	0.5	1.7
220.0	72.0	177.0	257.0	84.0	206.3	2.2	0.7	1.7
442.8	216.0	386.4	131.2	64.0	114.5	1.9	0.9	1.7
71.3	25.7	71.8	229.0	80.5	222.8	1.7	0.6	1.7
143.5	50.8	138.6	128.7	45.6	124.3	1.9	0.6	1.7

catheter was inserted under fluoroscopic control by way of an antecubital vein, the superior vena cava, the right atrium, and the inferior vena cava into a right hepatic vein.[10] Samples of hepatic venous and peripheral venous blood were taken at ten- to thirty-minute intervals throughout the study. Two or more urine collections were made for the determination of clearances and three or more blood samples were obtained for BSP determinations before and during a period of anesthesia with thiopental, cyclopropane or ether. Operation was then begun and measurements of clearance and EHBF were made less frequently. (In 11 subjects the study was continued for one to three hours postoperatively. Since many patients were given meperidine and atropine preparatory to operation, special studies of the effects of these agents were undertaken in 12 persons who were not subjected to other pharmacologic agents.) Arterial pressures were obtained throughout by sphygmomanometer or directly by a Lilly inductance manometer recording through a Brush magnetic oscillograph. Anoxia, respiratory difficulty, vomiting, and struggling were seldom encountered and probably did not contribute to the results to be presented. Surgical anesthesia was maintained at the second plane in as uniform a manner as the usual clinical criteria permitted.

Inulin and PAH were determined in diluted aliquots of urine and protein-free filtrates of plasma (precipitated with cadmium sulfate) by methods outlined elsewhere.[11] Bromsulfalein levels in plasma and infusion were determined colorimetrically.[10] Clearances were calculated in the usual manner from the urinary excretion and the plasma concentrations of inulin and PAH.* The

*No correction has been made for body surface.

TABLE II. EFFECT OF CYCLOP

PATIENT	AGE (YEARS)	DIAGNOSIS	PROCEDURE	BP (MM. HG)	GFR (ML. PER MINUTE)	ERPF (ML. PER MINUTE)	F F (PER CENT)	V (ML. PER MINUTE)
E. J.	52	Duodenal ulcer (subtotal gastrectomy)	Control	100/70	72	390	18	4.1
			Anesthesia	130/90	4	11	37	0.1
			Operation	120/80	18	80	23	0.7
J. McC.	52	Duodenal ulcer (subtotal gastrectomy)	Control	122/70	96	575	17	1.0
			Anesthesia	158/100	46	174	26	0.3
S. D.**	53	Duodenal ucler (subtotal gastrectomy)	Control	110/70	78	318	25	0.3
			Anesthesia	158/80	37	125	29	0.1
			Operation	160/88	57	138	41	0.2
			Recovery	80/60	113	485	23	0.9
F. S.	52	Duodenal ulcer (subtotal gastrectomy)	Control	130/80	147	712	20	0.6
			Anesthesia	146/80	18	61	29	0.05
			Operation	160/90	84	294	29	0.2
			Recovery	105/65	123	438	28	0.6
D. L.**	47	Chronic cholecystitis (cholecystectomy)	Control	108/60	62	428	15	0.6
			Anesthesia and operation	140/74	25	80	31	0.9
			†Recovery	114/84	69	270	26	0.3
A. K.	68	Chronic cholecystitis (cholecystectomy)	Control	170/76	101	502	20	3.1
			Anesthesia	182/80	66	232	28	0.6
V. G.**	43	Ventral hernia (herniorraphy)	Control	126/70	109	625	17	1.8
			Anesthesia	140/84	59	200	30	0.2
			Operation	140/80	68	223	31	0.2
			Recovery	110/70	132	545	24	0.6
A. Wa.**	39	Inguinal hernia (herniorraphy)	Control	110/70	80	371	21	1.1
			Anesthesia	120/70	40	128	32	0.1
			Operation	122/80	77	300	26	0.4
			Recovery	90/70	107	472	23	1.3
N. S.	29	Inguinal hernia (herniorraphy)	Control	122/80	92	499	18	0.6
			Anesthesia	126/74	45	174	26	0.1
			Operation	120/70	65	236	28	0.1
			Recovery	70/42	88	361	24	0.4
A. W.**	49	Inguinal hernia (herniorraphy)	Control	110/64	85	423	20	0.6
			Anesthesia	130/70	68	232	29	0.2
			Operation	130/80	62	201	31	0.2
			Recovery	100/60	75	340	22	0.4
M. R.**	52	Inguinal hernia (herniorraphy)	Control	116/60	67	269	25	1.7
			Anesthesia	110/60	33	97	34	0.6
			Operation	146/70	26	118	22	0.5

*See footnote, Table I.

**Meperidine, 100 mg. subcutaneously, given prior to this study.

†Ephedrine, 50 mg., given during this period (15 mg. intravenously and 35 mg. intramuscularly).

plasma concentrations used in these calculations were obtained by interpolation from graphs of the observed values plotted semilogarithmically against time, allowing two and one-half minutes for dead space time. Bromsulfalein concentrations were obtained similarly and EHBF was calculated according to the method described at length in another publication.[10] An internal lithium standard flame photometer was used for the analysis of sodium and potassium. Chloride was determined by the Schales and Schales method.[12] The oxygen content of arterial and hepatic venous blood collected anaerobically was measured on two occasions by the method of Van Slyke and Neill.[13]

RESULTS

The results of this investigation are tabulated in Tables I to V. In the first 4 tables data obtained in studies of renal function are presented accord-

ROPANE AND OF OPERATION ON RENAL FUNCTION*

U_{Na} (MEQ. PER LITER)	U_K (MEQ. PER LITER)	U_{Cl} (MEQ. PER LITER)	$U_{Na}V$ (μEQ. PER MINUTE)	U_KV (μEQ. PER MINUTE)	$U_{Cl}V$ (μEQ. PER MINUTE)	$U_{Na}V/GFR$ (μEQ. PER ML.)	U_KV/GFR (μEQ. PER ML.)	$U_{Cl}V/GFR$ (μEQ. PER ML.)
49.0	14.2	49.0	200.0	58.4	202.0	2.7	0.8	2.8
9.9	9.2	6.1	1.5	1.4	0.9	0.3	0.3	0.2
11.4	12.3	1.7	7.8	8.4	1.2	0.4	0.5	0.06
53.0	81.0	40.0	54.0	85.0	42.0	0.6	0.8	0.4
63.6	101.2	33.8	20.0	32.0	10.7	0.4	0.7	0.2
79.0	145.0	75.9	27.7	51.0	26.6	0.4	0.7	0.3
94.0	157.0	89.0	13.5	22.4	12.7	0.4	0.6	0.3
19.0	72.5	35.0	3.5	13.3	6.5	0.06	0.2	0.1
79.8	157.8	91.3	71.7	141.7	82.0	0.6	1.3	0.7
121.4	77.8	73.5	73.1	46.5	44.3	0.5	0.3	0.3
65.4	344.0	79.5	3.2	16.9	3.9	0.2	0.9	0.2
22.2	52.0	34.8	4.8	11.3	7.6	0.06	0.1	0.1
18.7	152.2	73.3	10.7	87.6	42.2	0.08	0.7	0.3
22.1	61.6	38.9	12.8	36.0	23.2	0.2	0.6	0.3
39.6	85.8	39.6	3.5	7.5	3.5	0.1	0.3	0.1
70.5	117.9	69.6	22.0	36.8	21.7	0.3	0.5	0.3
57.7	16.7	46.9	180.0	52.0	145.0	1.7	0.5	1.4
15.6	35.4	29.7	9.8	22.0	18.6	0.1	0.3	0.3
98.8	64.2	114.0	180.0	117.0	207.0	1.6	1.1	1.9
95.0	193.6	201.8	19.6	40.0	41.6	0.3	0.7	0.7
47.7	126.4	94.0	10.8	28.7	21.3	0.2	0.4	0.3
93.9	59.1	55.1	61.4	38.6	36.0	0.5	0.3	0.3
123.5	48.2	122.1	137.8	53.0	136.4	1.7	0.6	1.6
105.6	113.3	180.4	13.2	14.2	22.5	0.3	0.4	0.6
118.4	43.4	113.6	52.0	19.0	49.8	0.7	0.2	0.7
115.9	44.8	103.6	146.3	56.7	130.7	1.4	0.5	1.2
128.9	61.5	108.7	80.0	37.0	68.3	0.9	0.4	0.7
52.8	146.3	119.9	7.3	20.2	16.5	0.2	0.4	0.4
95.1	171.0	201.7	13.0	23.3	27.5	0.2	0.4	0.4
108.0	108.0	183.6	46.6	46.6	79.2	0.5	0.5	0.9
291.0	177.0	251.0	166.5	82.0	141.0	2.0	0.9	1.6
69.7	160.7	149.8	10.5	24.1	22.5	0.2	0.4	0.3
54.6	102.0	113.0	13.5	25.2	27.8	0.2	0.4	0.4
241.0	102.7	215.6	99.0	42.2	88.5	1.3	0.6	1.2
93.2	103.7	79.6	158.0	175.9	135.0	2.4	2.6	2.0
32.6	82.4	36.7	20.2	51.0	22.8	0.6	1.6	0.7
24.0	89.6	30.6	12.0	43.4	14.9	0.4	1.7	0.6

ing to the anesthetic agents employed. In each the data are arranged similarly to show the behavior of arterial pressure (spygmomanometric), glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF), urine flow (V), the urinary ionic concentration of sodium (U_{Na}), chloride (U_{Cl}), and potassium (U_K), the urinary excretion of sodium ($U_{Na}V$), chloride ($U_{Cl}V$), and potassium (U_KV), and the ratios between excretion of each of these electrolytes and the filtration rate. A single "control" figure is given for each subject, which is an average of two or more urine collection periods obtained just prior to anesthesia. The values during "anesthesia" or drug action and "operation" are single values showing the maximal effect observed. On several occasions noted in the tables as "anesthesia and operation," it was impossible to obtain measurements during anesthesia alone. The determinations during

"recovery" are those made immediately after termination of anesthesia and operation. These recovery periods usually lasted from ten to twenty minutes, depending upon the rate of urine flow. Carry-over of urine from the last period collected during operation may have obscured the return of the figures toward the control levels but most certainly did not operate to magnify the observed change.

Effect of Meperidine, Morphine, and Atropine.—Since many subjects were prepared for operation with meperidine and atropine, it was necessary to examine the effect of these agents alone. The data obtained in a study of meperidine in eight subjects are summarized in Table I. With one exception, all were free of renal or cardiovascular disease. In the exceptional case (Patient C. B.) the only clinical evidence of disease was occasional dependent edema, which was not present at the time of study. Meperidine was administered subcutaneously in 100 mg. doses, except in Patient A. S., who received 50 mg. Filtration decreased in all but 2, of whom one was Patient A. S. Filtration fell from 21 to 45 per cent below the control value. The effective renal plasma flow also decreased significantly from 24 to 50 per cent. The decrement in ERPF was associated with a slight rise in filtration fraction. These changes could not be ascribed to the slight and inconstant fall in blood pressure and they may be interpreted as evidence of intrarenal vasoconstriction. Similar but much less marked changes in clearances were observed in two subjects after administration of morphine sulphate, 10 mg. subcutaneously.

The urine flow always decreased after administration of meperidine or morphine, particularly during a water diuresis (Patients W. G., C. B., K. A., M. V., and A. S. in Table I). The decrement in water output was usually associated with increased urinary concentrations of sodium, potassium, and chloride. Despite this change, the output of all electrolytes diminished. The fall in urinary excretion of sodium was greater than the fall in filtration so that the ratio between excretion and filtration usually decreased. Chloride excretion behaved similarly. Potassium output was nearly always reduced to exactly the same extent as filtration. Since the urinary concentration of inulin rose, it may be inferred that tubular reabsorption of water, sodium, and chloride increased relative to filtration, whereas potassium reabsorption remained relatively unchanged. These changes were, in many respects, unlike those occurring during anesthesia. It was concluded, therefore, that the effects of anesthesia and operation would not be altered or obscured by prior medication with meperidine. Similarly, atropine (0.5 mg.) had no effect on renal function in two studies. When these agents were administered after the beginning of measurements of renal function, the values obtained in urine collection periods just prior to anesthesia were averaged and used as control figures. For this reason the values given for Patients A. W. and A. Wa. in Table I differ from those appearing in Table II, where the control figures are based upon averages of all the periods during the action of meperidine just before induction of anesthesia.

Effect of Cyclopropane and Operation.—Changes in renal function during cyclopropane anesthesia and major surgical procedures were examined in 11 patients. Four underwent subtotal gastrectomy; two, cholecystectomy; and the

remainder, herniorrhaphy. All were in good health, though one (Patient A. K.) presented evidence of uncomplicated essential hypertension and arteriosclerosis. Six had been given meperidine (100 mg.) and atropine (0.5 mg.) prior to study. The others had received only atropine (0.5 mg.). The effect of anesthesia alone was studied in Patients J. McC. and A. K. In the remainder the effects of operation and anesthesia were determined. The measurements were made following completion of operation and cessation of anesthesia in seven. As expected, the control urine flow and electrolyte excretion were usually depressed in those subjects receiving meperidine prior to study, but this phenomenon did not affect the response to cyclopropane.

The glomerular filtration rate, effective renal plasma flow, and the output of water and electrolytes invariably decreased to a striking degree immediately or shortly after induction of anesthesia. The fall in filtration was usually less marked than that in effective renal plasma flow, so that the filtration fraction rose. In view of the magnitude of the PAH clearance values, even when greatly reduced, the similarity and equality of the changes in PAH and inulin clearances, and the level of the filtration fractions, it seems unlikely that PAH extraction was impaired. Moreover, measurements of PAH extraction have failed to reveal any significant change under these conditions.[14] Hence the fall in ERPF probably indicates a similar fall in renal blood flow. Since it occurred in association with a slight elevation of arterial pressure, it is evident that there was a marked intrarenal vasoconstriction, presumably affecting both afferent and efferent arterioles. The surgical procedure appeared to have no further effect. Indeed, the clearance values often tended to rise somewhat as the operation went on.

In a few instances urine flow almost ceased entirely and in all it remained at a very low level throughout. The inulin concentration tended to rise but the concentrations of sodium and chloride always fell to very low levels. The urinary potassium concentration decreased in 5 and rose in 6 instances. Almost without exception, the output of sodium, chloride, and potassium ions decreased more than filtration so that the ratios fell. These changes indicate a relative increase in tubular reabsorption of water and electrolytes.

Following cessation of anesthesia, all values quickly returned to or close to the control levels (Table II and Fig. 1). As a rule the blood pressure fell during this phase, in a few instances to levels as low as those encountered in shock (Patients S. D. and N. S.). Nonetheless, the effective renal plasma flow and glomerular filtration rate increased. The calculated renal vascular resistance returned to the basal values. No evidence of reactive hyperemia of the kidneys was obtained. With the resurgence of glomerular filtration, urine flow and the output of electrolytes increased. There was little tendency to rise above the control values, however.

Effect of Ether and Operation.—The effect of ether anesthesia was studied in six subjects (Table III), four of whom were subjected to subtotal gastrectomy, one to lumbar sympathectomy for thromboangiitis obliterans, and one to inguinal herniorrhaphy.

In general, the behavior of glomerular filtration, effective renal plasma flow and urine output closely resembled that during the course of cyclopropane anesthesia, though the response was not quite so marked. Filtration and effective renal plasma flow decreased shortly after the establishment of anesthesia in

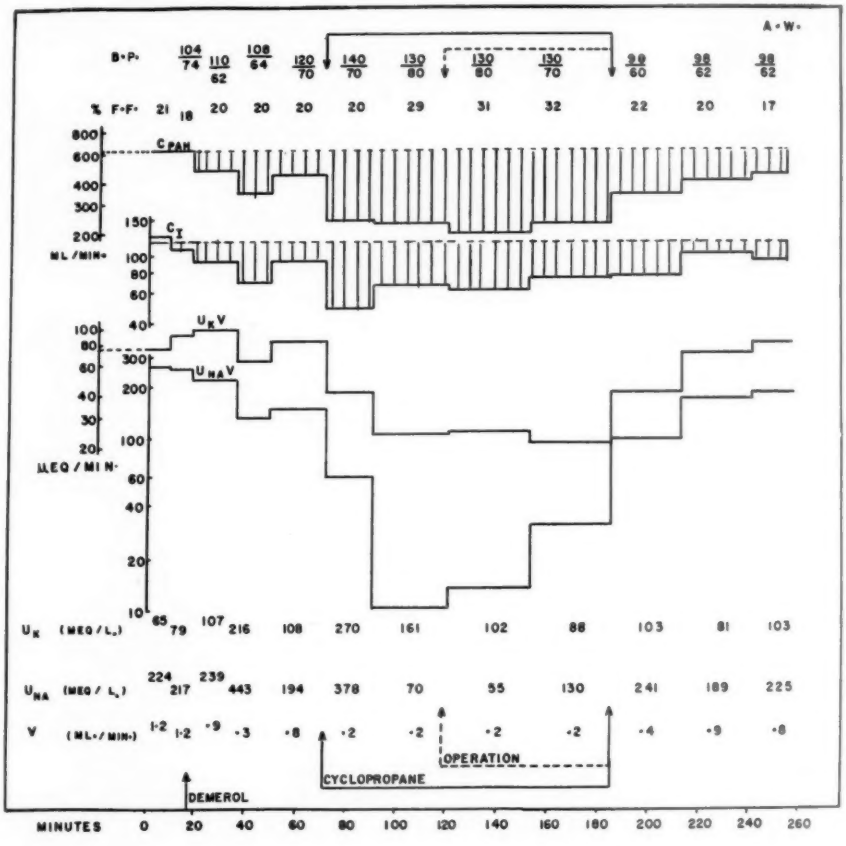

Fig. 1.—Effect of meperidine and cyclopropane on renal functions.

The arterial pressure (BP) was measured sphygmomanometrically at intervals throughout this study and the values given here appeared to be representative for the period indicated. The renal plasma flow (milliliters per minute) was measured by para-aminohippurate clearance (C_{PAH}) and glomerular filtration rate by inulin clearance (C_I). An average of the values for the first two collection periods was used as the control level and served as a basis for the straight broken base line. The filtration fraction (FF-per cent) was calculated by dividing C_I by C_{PAH} and multiplying by 100. The urinary excretion of potassium (U_KV) or sodium ($U_{Na}V$) was calculated in microequivalents per minute from the urinary concentration of potassium (U_K-milliequivalents per liter) or of sodium (U_{Na}-milliequivalents per liter) and from the urine flow (V-milliliters per minute). All values are plotted semilogarithmically against time (minutes) in order to show percentile changes graphically.

The patient (A. W.), a 49-year-old Negro man in excellent health, was admitted for repair of a recurrent right inguinal hernia. Breakfast was withheld but no drugs were given prior to the study. After obtaining two control values, meperidine 100 mg. and atropine 0.5 mg. were given intramuscularly (at the time indicated by the arrow and "Demerol"). It can be seen that C_{PAH}, C_I, $U_{Na}V$, and U_KV decreased and U_{Na} and U_K rose. Urine flow fell off markedly and then showed a tendency to rise. At this point cyclopropane anesthesia was induced (at the arrow and "cyclopropane") and it can be seen that all values fell sharply with the exception of the arterial pressure, which increased somewhat. After two periods, operation (broken arrow and "Operation") was started without significant effect. Indeed, the output of sodium tended to rise. Following the simultaneous termination of anesthesia and operation, all values began to return to the base line, (both $U_{Na}V$ and U_KV rise and lines in figure do not cross), though the arterial pressure fell precipitiously as a result of "cyclopropane shock." This condition was not associated with any other evidences of circulatory collapse since the pulse was slow and full, the skin was warm, and it can be seen that renal plasma flow was depressed no more than was expected on the basis of hypotension alone; that is, renal vasoconstriction, a constant concomitant of traumatic shock, was absent. The patient regained consciousness but did not complain of pain or other symptoms before the end of the first period postoperatively.

association with a fall in water and electrolyte excretion. The tubular reabsorption of water, sodium, and chloride increased relative to filtration. The urinary concentration of sodium and chloride did not fall as regularly after ether as after cyclopropane. Potassium excretion fell off to approximately the same extent as filtration. Again it may be seen that operation had little or no effect. Ephedrine was used in Patient M. L. (Table III) to maintain the blood pressure during operation. The resulting elevated pressure levels were associated with augmented clearances. With cessation of anesthesia and recovery, all values tended to return quickly toward the control levels, though this did not occur in Patient H. A. until the period subsequent to that presented in the table (Table III).

Effect of Thiopental and Operation.—The data collected in a study of the effect of thiopental on renal function are presented in Table IV. Five patients (two subjected to subtotal gastrectomy and three to herniorrhaphy) are included here. Recovery from thiopental anesthesia was studied in one patient. It can be seen that these patients showed a response which was similar to that produced by cyclopropane and ether. All values fell promptly following induction, with little further alteration during operation. Electrolyte and water reabsorption increased. Recovery was almost complete within a very short time after completion of operation and withdrawal of the anesthetic agent.

DISCUSSION

General anesthetic agents appear to have a profound but more or less uniform and nonspecific effect upon urine formation and renal hemodynamics. Essentially the same responses were observed in these studies during anesthesia with cyclopropane, thiopental, or ether. As shown in the tables, these changes were large, readily reversible, and distinctive.

Fig. 1 illustrates graphically this response in its entirety. Meperidine (Demerol), given after two control periods, evoked a brief reduction in glomerular filtration (C_I) and ERPF (C_{PAH}), apparently as a result of intrarenal vasoconstriction. Simultaneously, the urine flow (V) fell abruptly from 1.2 ml. to 0.3 ml. per minute and the output of sodium ($U_{Na}V$), potassium (U_KV), and chloride (not shown) in the urine diminished, but not to the same extent as the urine flow. Hence, the urinary concentrations of these substances rose. Cyclopropane anesthesia evoked a much more striking response than meperidine. Both filtration and renal plasma flow decreased still further and urine flow fell in association with a sharp drop in urinary sodium (U_{Na}) and chloride concentrations. Potassium concentration (U_K) also decreased, but not as much as sodium. The filtration fraction (FF) tended to rise because the PAH clearance or effective renal plasma flow fell more than filtration. This decrement in renal blood flow occurred at a time when arterial pressure had increased somewhat and it may be presumed that intrarenal vasoconstriction occurred. Operation (herniorrhaphy) produced no additional detrimental change in renal function. Indeed, sodium output and urinary concentration tended to rise somewhat. With termination of anesthesia and operation, all values tended to return to the base line level. Despite a definite fall in arterial pressure (BP)

TABLE III. EFFECT OF ETHER AND

PATIENT	AGE (YEARS)	DIAGNOSIS	PROCEDURE	BP (MM. HG)	GFR (ML. PER MINUTE)	ERPF (ML. PER MINUTE)	F F (PER CENT)	V (ML. PER MINUTE)
F. P.**	63	Inguinal hernia (herniorraphy)	Control	114/70	79	403	20	7.2
			Anesthesia	126/80	61	285	21	4.9
			Operation	110/62	77	277	28	5.1
M. L.**	43	Thromboangiitis obliterans (lumbar symathectomy)	Control	120/70	167	636	27	0.9
			†Anesthesia and operation	120/72	62	163	38	0.2
			Recovery	110/64	119	524	23	1.8
M. C.**	59	Duodenal ulcer (subtotal gastrectomy)	Control	108/70	118	530	22	0.4
			Anesthesia	120/72	82	315	26	0.2
			Operation	120/74	38	201	19	0.1
			Recovery	120/70	145	948	15	0.9
J. W.**	61	Duodenal ulcer (subtotal gastrectomy)	Control	130/80	69	215	32	0.3
			Anesthesia	140/78	29	84	34	0.1
I. E.	41	Duodenal ulcer (subtotal gastrectomy)	Control	120/70	130	613	21	1.9
			Anesthesia	135/75	92	236	39	0.5
			Operation	120/70	121	382	32	0.9
H. A.**	45	Duodenal ulcer (subtotal gastrectomy)	Control	130/80	131	572	23	1.0
			Anesthesia	160/84	90	296	31	0.5
			Operation	190/90	90	408	22	0.5
			Recovery	155/86	76	456	17	0.4

*See footnote, Table I.

**Meperidine, 100 mg. subcutaneously, given prior to this study.

†Ephedrine, 50 mg., given during this period (15 mg. intravenously and 35 mg. intramuscularly).

TABLE IV. EFFECT OF THIOPENTAL AND

PATIENT	AGE (YEARS)	DIAGNOSIS	PROCEDURE	BP (MM. HG)	GFR (ML. PER MINUTE)	ERPF (ML. PER MINUTE)	F F (PER CENT)	V (ML. PER MINUTE)
N. K.**	69	Inguinal hernia (herniorraphy)	Control	140/80	68	312	22	1.9
			Anesthesia and operation	130/90	46	203	23	0.5
A. D.**	36	Inguinal hernia (herniorraphy)	Control	130/80	114	574	20	1.4
			Anesthesia	110/76	80	337	24	0.7
			Operation	110/80	81	269	30	0.7
J. E.	47	Duodenal ulcer (subtotal gastrectomy)	Control	130/74	77	352	21	3.5
			Anesthesia and operation	132/70	59	298	20	0.9
L. H.	59	Duodenal ulcer (subtotal gastrectomy)	Control	168/88	100	469	21	4.4
			Anesthesia	98/78	30	285	10	0.5
			Operation	118/62	28	265	10	0.6
W. W.	28	Inguinal hernia (herniorraphy)	Control	114/76	123	566	22	0.8
			Anesthesia	110/72	116	452	26	1.0
			Operation	108/70	99	166	59	0.3
			Recovery	118/80	429	429	29	0.4

*See footnote, Table I.

**Morphine 12 mg., given prior to control.

Control values on N. K. and A. D. are taken from single periods prior to anesthesia, whereas the control values on J. E. and L. H. are averages of 3 periods.

OPERATION ON RENAL FUNCTION*

U_{Na} (MEQ. PER LITER)	U_K (MEQ. PER LITER)	U_{Cl} (MEQ. PER LITER)	$U_{Na}V$ (μEQ. PER MINUTE)	U_KV (μEQ. PER MINUTE)	$U_{Cl}V$ (μEQ. PER MINUTE)	$U_{Na}V$/GFR (μEQ. PER ML.)	U_KV/GFR (μEQ. PER ML.)	$U_{Cl}V$/GFR (μEQ. PER ML.)
58.0	12.0	57.1	415.0	86.6	411.8	5.2	1.1	5.1
43.6	10.5	45.1	213.9	51.3	221.0	3.5	0.8	3.6
22.7	14.1	27.9	115.3	71.5	141.1	1.5	0.9	1.8
113.0	92.0	116.8	101.1	82.3	104.8	0.6	0.5	0.6
40.7	127.4	63.7	9.9	31.2	15.6	0.2	0.5	0.4
72.6	62.6	80.6	133.4	115.0	148.0	1.1	0.9	1.2
75.8	73.0	93.4	34.0	32.5	42.0	0.3	0.3	0.3
102.0	158.0	174.0	17.8	27.5	30.3	0.2	0.3	0.4
29.5	76.0	46.0	3.7	9.5	5.8	0.1	0.4	0.2
48.8	102.6	26.9	42.7	89.8	23.5	0.3	0.6	0.2
38.9	79.4	32.4	9.8	26.0	10.7	0.1	0.4	0.1
38.4	65.4	44.4	5.3	9.0	6.0	0.2	0.3	0.2
130.4	61.1	72.1	246.0	115.2	136.0	1.9	0.9	1.0
33.3	25.6	27.7	17.7	13.6	9.5	0.2	0.1	0.1
40.8	26.0	48.9	35.5	22.6	42.5	.0.3	0.2	0.4
71.4	55.0	66.4	70.0	54.3	65.0	0.5	0.4	0.5
70.5	69.7	74.7	33.0	32.6	35.0	0.4	0.4	0.4
30.4	112.2	38.8	15.6	57.7	19.9	0.1	0.6	0.2
20.5	137.0	22.8	8.9	59.4	9.9	0.1	0.7	0.1

OPERATION ON RENAL FUNCTION*

U_{Na} (MEQ. PER LITER)	U_K (MEQ. PER LITER)	U_{Cl} (MEQ. PER LITER)	$U_{Na}V$ (μEQ. PER MINUTE)	U_KV (μEQ. PER MINUTE)	$U_{Cl}V$ (μEQ. PER MINUTE)	$U_{Na}V$/GFR (μEQ. PER ML.)	U_KV/GFR (μEQ. PER ML.)	$U_{Cl}V$/GFR (μEQ. PER ML.)
87.7	24.5	102.4	168.0	46.9	196.3	2.5	0.7	2.9
44.4	57.9	67.5	23.9	31.1	36.3	0.5	0.7	0.8
257.0	34.9	124.3	364.6	49.6	176.3	3.2	0.4	1.6
52.1	46.0	75.2	34.0	30.0	49.1	0.4	0.4	0.6
3.5	39.1	32.0	2.6	28.6	23.4	0.3	0.4	0.3
42.6	28.6	66.4	151.0	100.0	234.0	1.9	1.3	3.0
76.2	27.8	19.1	68.1	24.9	17.1	1.2	0.4	0.3
22.5	9.5	18.5	101.2	40.1	81.4	1.1	0.5	0.9
61.2	32.2	0.8	31.5	16.6	0.4	1.1	0.6	0.01
32.0	21.8	0.8	19.7	13.5	0.5	0.7	0.5	0.02
82.0	65.8	102.5	59.4	49.6	77.1	0.5	0.4	0.6
29.7	46.4	55.8	29.8	46.4	55.8	0.3	0.4	0.5
9.3	64.8	58.7	2.4	16.7	15.1	0.02	0.2	0.2
109.0	141.6	156.5	47.2	61.2	67.7	0.4	0.5	0.5

the PAH clearance returned almost to the preoperative and pre-meperidine values. Calculation of renal vascular resistance revealed complete reversal of vasoconstriction which had developed during the action of meperidine and cyclopropane. Hence, PAH clearance was depressed postoperatively no more than it should have been as a result of the hypotension alone.

The renal hemodynamic response to anesthesia apparently consists of vasoconstriction that persists only so long as consciousness is obtunded by ether, cyclopropane, or thiopental. Since filtration is affected to almost the same extent as renal blood flow, it may be surmised that both afferent and efferent arteriolar constriction accounts for the increased renal vascular resistance. On two occasions (Table II, Patient E. J., and Table IV, Patient W. W.) the value for PAH fell to extremely low levels and filtration fraction rose disproportionately. It must be assumed that vasoconstriction was associated with impaired tubular function and reduced renal extraction of PAH in these instances, but for the most part the PAH clearance may be accepted as a valid measure of renal plasma flow.

TABLE V. EFFECT OF THIOPENTAL AND OF CYCLOPROPANE ON ESTIMATED HEPATIC BLOOD FLOW (EHBF), OXYGEN, AND BROMSULFALEIN UPTAKE*

PATIENT	AGE	DIAGNOSIS	ANESTHESIA	BP (MM. HG)	P_{BSP} (MG. PER CENT	E_{BSP} (PER CENT)	EHBF (ML. PER MINUTE	O_2 A-V DIFFERENCE (ML. PER CENT
J. B.	47	Duodenal ulcer	Control	120/80	0.72	65	1730	
			Thiopental	100/70	0.99	36	1990	
A. B.	41	Inguinal hernia	Control	118/60	1.32	42	1390	3.3
			Thiopental	100/54	2.22	34	830	5.2
E. J.	52	Duodenal ulcer	Control	124/70	1.05	22	2500	
			Cyclopropane	130/90	1.17	31	1084	
T. N.	34	Interval appendix	Control	108/64	1.00	52	1480	
			Cyclopropane	130/90	0.96	78	860	
L. S.	50	Lipoma of neck	Control	154/90	2.04	26	1810	5.9
			Cyclopropane	180/88	3.25	37	820	9.9

*With few exceptions these values are averages of 2 or more observations. P_{BSP}, peripheral venous plasma concentration of bromsulfalein; E_{BSP}, hepatic extraction of BSP; EHBF, estimated hepatic blood flow; O_2 A-V Difference, hepatic oxygen arteriovenous difference; and BP, arterial pressure.

The vasoconstrictive response in the renal vascular bed was associated with evidence of vasoconstriction in the splanchnic circulation. Table V contains the data collected in a study of the action of thiopental and of cyclopropane on the splanchnic circulation in 5 subjects. With a single exception (Patient J. B., Table V) EHBF fell during anesthesia out of proportion to any tendency of the blood pressure to fall or in association with an elevation of blood pressure indicating vasoconstriction in the splanchnic bed. In Patient J. B. simultaneous determination of renal blood flow also failed to show any change until shortly after the last measurement of EHBF, and it may be surmised that given sufficient time EHBF would also have decreased in this patient. It may be noted that the hepatic extraction of BSP (E_{BSP}) tended to rise as EHBF fell during cyclopropane anesthesia, suggesting that the reduction in the flow of blood through the liver resulted in a more prolonged contact between extracting cells

and blood containing BSP and thus permitted more efficient extraction. This view finds additional support in the observation that hepatic oxygen uptake increased sharply during the period of ischemia, indicating, in addition, little or no alteration in oxygen consumption. It is possible that thiopental interferes directly witih hepatocellular activity to some extent, accounting here for the fall observed in BSP extraction.

The causes for these vascular readjustments are difficult to determine. It is evident that the traumatic stimulus of the operative procedure had little or no influence regardless of whatever effect it might have had in the absence of anesthesia and it may be surmised that even then pain and fear would play a major role in exciting renal and splanchnic vascular responses. The rapid reversal of the renal vasoconstriction following termination of anesthesia suggests that the drugs have little significant direct action since the tissue concentration probably did not change as promptly as the concentration in the blood and the effect should therefore have persisted.[15] It is extremely interesting that the changes in renal and hepatic vascular resistance resemble those observed during shock, chronic anemia, congestive heart failure, pain, violent exercise, or orthostasis; that is, situations in which visceral vasoconstriction serves a homeostatic purpose in diverting blood temporarily from organs where it is not immediately required to regions, such as brain and heart, that are dangerously sensitive during stress to oxygen lack.[16-22] But even if the vascular response to anesthesia is to be regarded as a homeostatic response to stress, the mechanisms by which it is mediated and produced remain obscure. There is no consistent change in blood pressure to which this role may be assigned. Preliminary studies indicate that interruption of the usual autonomic pathways by sympathectomy or high spinal anesthesia does not alter readjustments during cyclopropane, ether, or thiopental anesthesia. A humoral agent which quickly appears in the circulating blood after induction of anesthesia and clears as rapidly on recovery cannot be eliminated as a possible cause.

The derangement in urine formation following administration of meperidine or morphine may be ascribed in the main to the release of antidiuretic hormone (ADH) by the posterior pituitary, since de Bodo[23] has shown that the antidiuretic effect of morphine is abolished in dogs by neurohypophysectomy. This view finds support in the fact that water excretion was preponderantly affected (Table I). During general anesthesia, however, the electrolyte excretion was much more profoundly disturbed, indicating that additional factors were involved. The plasma concentrations of sodium, potassium, and chloride measured during these studies often decreased somewhat, but never to an extent commensurate with the reduction observed in renal excretion. The fall in glomerular filtration resulting from intrarenal vasoconstriction is a more likely cause for this phenomenon. Numerous studies have shown that a reduction in filtration results in a relative increase in tubular reabsorption of electrolytes and water.[25, 26] Moreover, abdominal compression produces this effect even in patients with well-established and uncontrolled diabetes insipidus.[27] It is probable that the retarded flow of filtrate down the renal tubules permits

more effective reabsorption of solutes and water, regardless of the needs of the body and the state of endocrine activation, thus producing oliguria and diminished excretion of electrolytes as long as filtration is low.

The apparent correction of the disturbance in urine formation in association with the return of filtration to the control levels almost immediately after termination of anesthesia is in harmony with this explanation. Nonetheless, it has been shown that administration of water and salt in the immediate postoperative period may give rise to edema because of the failure of the kidneys to make appropriate regulatory adjustments.[28] The studies reported here indicate that persistent impairment of filtration does not account for this defect and suggest that the tubules have been conditioned in some manner by anesthesia and operation so that excretion of water and salt loads is prevented or delayed. It is possible that oversecretion of adrenal cortical hormones or local tubular cellular changes secondary to prolonged vasoconstriction and relative anoxia may ultimately prove to be at fault.

SUMMARY

Measurements of glomerular filtration rate (inulin clearance), urinary sodium, potassium and chloride excretion, renal blood flow (PAH clearance), and estimated hepatic blood flow (bromsulfalein method) were made in thirty-four human subjects before and during the action of meperidine, cyclopropane, ether, or thiopental anesthesia, major surgical procedures, and the immediate postoperative period.

Meperidine (100 mg. subcutaneously in 7 subjects and 50 mg. in 1 subject) invariably caused a marked depression in urine flow and electrolyte excretion. The urinary concentration of the electrolytes usually increased. Glomerular filtration and renal plasma flow decreased as a result of intrarenal vasoconstriction.

General anesthesia with cyclopropane, ether, or thiopental evoked a much more striking vasoconstrictive response in both the liver and kidney in association with a fall in filtration, urinary concentration and excretion of electrolytes and urine flow. As a rule, the output of electrolytes and water decreased more than filtration, indicating a relative augmentation in renal tubular reabsorption. Operation had little additional effect. All values returned to or almost to control levels shortly after termination of anesthesia, suggesting that postoperative retention of water and salt may be attributable to a tubular dysfunction.

We wish to acknowledge our indebtedness to Miss L. Fogel, Miss J. Hunt, and Miss R. Lipton for technical assistance and to Dr. J. F. Nickel, Dr. L. Brandt, Dr. W. D. Blake, and Dr. J. Craig for professional aid.

REFERENCES

1. Coller, F. A., Rees, V. L., Campbell, K. N., Iob, V. L., and Moyer, C. A.: Effects of Ether and Cyclopropane Anesthesia Upon the Renal Function in Man, Ann. Surg. **118:** 717-727, 1943.
2. Corcoran, A. C., and Page, I. H.: Effects of Anesthetic Dosage of Pentobarbital Sodium on Renal Function and Blood Pressure in Dogs, Am. J. Physiol. **140:** 234-239, 1943.
3. Craig, F. N., Visscher, F. E., and Houck, C. R.: Renal Function in Dogs Under Ether or Cyclopropane Anesthesia, Am. J. Physiol. **143:** 108-118, 1945.

4. Burnett, C. H., Bloomberg, E. L., Shortz, G., Compton, D. W., and Beecher, H. K.: A Comparison of the Effects of Ether and Cyclopropane Anesthesia on the Renal Function of Man, J. Pharmacol. & Exper. Therap. **96**: 380-387, 1949.
5. Selkurt, E. E.: Physiologic Mechanisms of the Kidneys in Relation to Anesthesia, Bull. Am. A. Nurse Anesth. **17**: 242-251, 1949.
6. Stewart, J. D., and Rourke, G. M.: Changes in Blood and Interstitial Fluid Resulting From Surgical Operation and Ether Anesthesia, J. Clin. Investigation **17**: 413-416, 1938.
7. Bonnycastle, D. D.: The Effect of Some Anesthetic Agents on the Volume of Body Fluid, J. Pharmacol. & Exper. Therap. **75**: 18-29, 1942.
8. Volpitto, P. P., Woodbury, R. A., and Hamilton, W. F.: Direct Arterial and Venous Pressure Measurements in Man as Affected by Anesthesia, Operation and Shock, Am. J. Physiol. **128**: 238-245, 1940.
9. Bennett, H. S., Bassett, D. L., and Beecher, H. K.: Influence of Anesthesia (Ether, Cyclopropane, Sodium Evipal) on the Circulation Under Normal and Shock Conditions, J. Clin. Investigation **23**: 181-208, 1944.
10. Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: The Estimation of Hepatic Blood Flow in Man, J. Clin. Investigation **24**: 890-897, 1945.
11. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J., and Blake, W. D.: Renal Function in Renal Diseases, Am. J. Med. **9**: 766-798, 1950.
12. Schales, O., and Schales, S. S.: A Simple and Accurate Method for the Determination of Chloride in Biological Fluids, J. Biol. Chem. **140**: 879-884, 1941.
13. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**: 523-573, 1924.
14. Breed, Ernest: Personal communication.
15. Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. A.: The Fate of Thiopental in Man and a Method for Its Estimation in Biological Material, J. Pharmacol. & Exper. Therap. **98**: 85-96, 1950.
16. Bradley, S. E.: Variations in Hepatic Blood Flow in Man During Health and Disease, New England J. Med. **240**: 456-461, 1949.
17. Lauson, H. D., Bradley, S. E., and Cournand, A.: The Renal Circulation in Shock, J. Clin. Investigation **23**: 381-402. 1944.
18. Bradley, S. E., and Bradley, G. P.: Renal Function During Chronic Anemia in Man, Blood **2**: 192-202, 1947.
19. Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients With Chronic Congestive Heart Failure: Evidence of "Forward Failure" as the Primary Cause of Edema, J. Clin. Investigation **25**: 389-400, 1946.
20. Wolf, G. A., Jr.: The Effect of Pain on Renal Function, A. Research Nerv. & Ment. Dis. Proc. **23**: 358-364, 1943.
21. Chapman, C. B., Henschel, A., Minckler, J., Forsgren, A., and Keys, A.: The Effect of Exercise on Renal Plasma Flow in Normal Male Subjects, J. Clin. Investigation **27**: 639-644, 1948.
22. Smith, H. W.: Lectures on the Kidney, Lawrence, Kan., 1943, University Extension Division, University of Kansas.
23. de Bodo, R. C.: The Antidiuretic Action of Morphine, and Its Mechanism, J. Pharmacol. & Exper. Therap. **82**: 74-85, 1944.
24. Ferrer, M. I., and Sokoloff, L.: The Antidiuretic Effect of Morphine and Demerol in Congestive Heart Failure, Am. J. M. Sc. **214**: 372-384, 1947.
25. Selkurt, E. E., Hall, P. W., and Spencer, M. P.: Graded Arterial Pressure Decrement and Renal Clearance of PAH, Creatinine and Sodium, Federation Proc. **8**: 143, 1949.
26. Pitts, R. F., and Duggan, J. J.: Studies on Diuretics. II. The Relationship Between Glomerular Filtration Rate, Proximal Tubular Absorption of Sodium and Diuretic Efficacy of Mercurials, J. Clin. Investigation **29**: 372-379, 1950.
27. Bradley, S. E., Mudge, G. H., Blake, W. D., and Alphonse, P.: The Effect of Increased Intra-abdominal Pressure Upon Renal Excretion of Water, Sodium and Potassium in Normal Human Subjects and in Patients With Diabetes Insipidus, J. Clin. Investigation **28**: 772, 1949.
28. Moyer, C. A.: Acute Temporary Changes in Renal Function Associated With Major Surgical Procedures, SURGERY **27**: 198-207, 1950.

CONSERVATISM IN THE SURGICAL TREATMENT OF BENIGN GASTRIC ULCER

FRANKLIN B. WILKINS, M.D.,* AND JOSEPH A. WEINBERG, M.D.,*
LONG BEACH, CALIF., AND JACK M. FARRIS, M.D.,**
LOS ANGELES, CALIF.

WEDGE or segmental resections of benign gastric ulcer combined with a gastric drainage procedure were used for many years as a treatment for peptic ulcer of the stomach. Walton,[1] in 1935, reported 310 patients in whom wedge excision combined with gastrojejunostomy was performed. There was a mortality of 4.2 per cent in this group. Those patients followed for a period of five years or more had a complete cure in 88 per cent of the cases. Only six of this group developed recurrent ulcers. Balfour and co-workers[2] reported 1,202 patients with gastric ulcers treated between 1906 and 1927 by local excision with or without a gastric drainage procedure, with a mortality rate of 3.8 per cent. In 574 of the patients with excisions combined with a gastric drainage procedure followed for two years or longer, 82.7 per cent were reported as "cured or much improved." They stated that the apparent advantages of the method were as follows: (1) it may be applied to a large percentage of gastric ulcers; (2) it is simple, speedy and safe; (3) The late results are at least the equal of any other method; (4) It can be used in cases in which no other means of attack upon the ulcer are justifiable.

It must be said, however, that subtotal gastrectomy has now replaced this more limited resection and has also been accepted by the majority of abdominal surgeons throughout the world as being the most satisfactory and successful treatment of gastric ulcer. The possibility exists that the addition of a vagotomy to the more conservative procedure may give equally as good results without sacrificing a major portion of the stomach. It is this possibility that led us to this present study.

Occasionally one may be confronted with an ulcer high on the lesser curvature or in juxtaposition to the esophagus which has failed to respond to the usual medical regimen. Because of the critical consideration of the presence or absence of cancer, the clinician, in this instance, is more or less obligated to carry out a rather formidable operation. It is not unusual to perform total gastrectomy, for example, only to find later that the ulcer is benign and partially healed.

There is a growing appreciation in the minds of clinicians that the underlying diathesis responsible for peptic ulceration of the stomach differs in some respects from that of duodenal peptic ulceration. In the former, gastric acids are somewhat lower, the age group is somewhat higher, and complications such as anastomotic ulcer are rare.

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*From the Department of Surgery, Veterans Administration Hospital, Long Beach.
**Consultant in Surgery, Veterans Administration Hospital, Long Beach.

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Neurosurgeons[3] are aware of the frequency of gastrointestinal hemorrhage subsequent to cranial operations. Hart[4] observed that 17 per cent of ulcers disclosed at autopsy were associated with intracranial pathology. Injections of Pitressin, of acetylcholine, of pilocarpine, and of adrenalin produce gastrointestinal ulceration or hemorrhage in animals.[5-9] Similarly, changes in function or structure of the gastrointestinal tract have been produced by stimulation or destruction of various parts of the central nervous sysem.[10] Wang, Clark, and associates[11] noted immediate blanching of the gastric mucosa and increased motility of the gastric musculature after stimulating the anterior hypothalmus.

The ulceration tendency in association with intracranial lesions is predominantly gastric rather than duodenal. These considerations suggest that certain gastric ulcers do not require subtotal gastrectomy for their cure and serve further as a background for this present clinical study. Thirty-two patients with gastric ulcers have been treated by conservative wedge or segmental resection; some have been afforded the presumed protection of vagus resection. These patients have been followed for a period of from two to thirty months.

METHOD OF STUDY

Thirty-two patients with benign gastric ulcers provide the clinical data for this study. The presence of the ulcer and its benign nature were proved at operation in every instance. There were thirty men and two women. One patient was in the third decade of life, five in the fourth, eight in the fifth, fourteen in the sixth, and four in the seventh decade.

SPECIAL PREOPERATIVE STUDIES

Gastroscopic examination was carried out in twenty of the thirty-two patients. In fourteen instances a benign ulcer was diagnosed and confirmed at operation. In four instances the ulcer was thought to be malignant by the gastroscopist, but this was not substantiated at operation. In two instances the gastroscopic examination failed to identify a gastric ulcer which was later proved to be present at operation.

TABLE I. GASTROSCOPIC FINDINGS IN TWENTY PATIENTS WITH PROVED GASTRIC ULCER

Benign ulcer diagnosed correctly	14 cases
Carcinoma diagnosed incorrectly	4 cases
Failure to reveal ulcer	2 cases

ROENTGENOLOGIC EXAMINATION

Gastrointestinal examinations were made on thirty-one of the thirty-two patients. The presence of a gastric ulcer was demonstrated in twenty-seven

TABLE II. PREOPERATIVE ACID IN 28 CASES

ANACIDITY 0°	HYPOACIDITY 1°-20°	NORMAL ACID 20°-40°	HYPERACIDITY 40°+
8	8	7	5

of the thirty-one cases. In two cases the diagnosis of ulcer was made by the gastroscopist after negative roentgenograms.* In the remaining two cases the presence of the ulcer was demonstrated at operation.

GASTRIC ANALYSIS

This examination was carried out in twenty-eight patients (Table II), utilizing the standard histamine stimulation technique. In eight patients there was anacidity, and in eight others hypoacidity (1° to 20°). Seven patients showed normal acid values (20° to 40°), and in five there was hyperacidity (40°+).

It will be noted that in over one-half of the gastric ulcer cases the fasting hydrochloric acid was either absent or below normal levels.

OPERATIVE PLAN

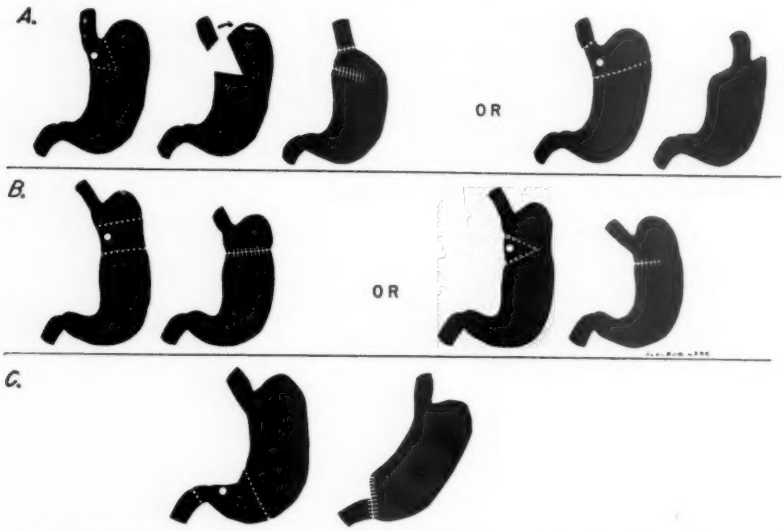


Fig. 1.—Operative plan. *A*, Wedge or segmental resection for benign gastric ulcer lying in proximity to the esophagus with preservation of the distal segment of the stomach. In certain instances this may require actual transplantation of the esophagus to the body of the stomach. *B*, **Left**: segmental resection of the stomach, preserving the cardia for anastomosis to the fundus and body. **Right**: wedge resection of the lesser curvature, including a benign gastric ulcer followed by simple closure. Resections in this area without pyloroplasty and irrespective of vagotomy will produce delayed emptying. *C*, Simple segmental resection for benign gastric ulcer in the pyloric region of the stomach, followed by anastomosis of the duodenum to the proximal gastric stump (Billroth I).

OPERATIVE PLAN

As one of the objectives of this study was to observe the result of vagotomy as an adjunct in the surgical management of gastric ulcer, various operative combinations were used. These included:

	NUMBER OF PATIENTS
1. Wedge resection + pyloroplasty	9
2. Wedge resection + vagotomy + pyloroplasty	10
3. Wedge or segmental resection + vagotomy	7
4. Wedge resection + vagotomy + gastroenterostomy	4
5. Wedge or segmental resection alone without vagotomy or drainage procedure	2
Total patients	32

*All gastroscopic studies were carried out by Dr. Rudolph Schindler and associates.

After a preliminary work-up on the medical service (including blood studies, gastric analyses, gastrointestinal x-ray studies, gastroscopic examinations) and an evaluation of medical management, the patients were transferred to the surgical service in preparation for operation. A thorough abdominal exploration was carried out through a transverse incision under spinal anesthesia. If the ulcer were located in the pylorus or prepyloric region, a segmental type of resection (Billroth I) was carried out. If the lesion was in an accessible portion of the lesser curvature, a generous wedge was removed. For ulcers in juxtaposition to the esophagus (although there were none in this series) it was decided that a conservative type of resection would be carried out at the cardia with anastomosis of the esophagus to the remaining distal gastric segment, thereby avoiding total gastrectomy (Fig. 1, *A*, *B*, and *C*).

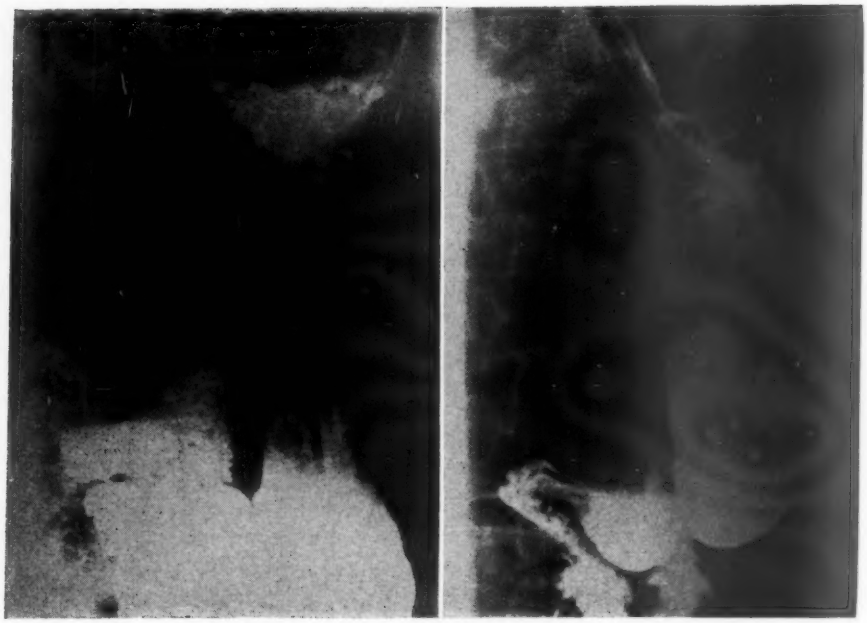
If a vagotomy was done, it was performed first. Vagus resection has been carried out in approximately two-thirds of the cases. A generous segment of the stomach including the ulcer was then removed and sent to the pathology laboratory for frozen sections. The report was available by the time the gastric defect was closed. If carcinoma was found, a high subtotal or total gastric resection was performed. If the diagnosis was a benign ulcer, no additional gastric tissue was removed. A gastric drainage procedure (Heineke-Mikulicz pyloroplasty or posterior gastroenterostomy) was then done in approximately two-thirds of the cases. To date there have been no discrepancies between the frozen sections and the permanent paraffin section diagnoses. The difficulties of frozen section diagnoses of mucous membrane lesions are well known. However, the pathologist is better able to give an accurate diagnosis when presented with the entire ulcer and surrounding gastric wall (as in wedge resection) than from conventional biopsies from the margin of the ulcer. It is appreciated that occasionally one may be confronted with situations where a benign diagnosis received at the operating table is later reversed. If subtotal resection had been carried out in such an instance on the assumption that the ulcer was benign, only later to find it was malignant, it would be desirable to reoperate—and perhaps mandatory if neoplasm were identified at the cut margin of the specimen. Reoperation would be more hazardous and difficult than if wedge or segmental resection had been done. In other words, the technical aspects of converting a subtotal resection to a complete or almost complete one are more difficult than conversion after wedge or segmental resection.

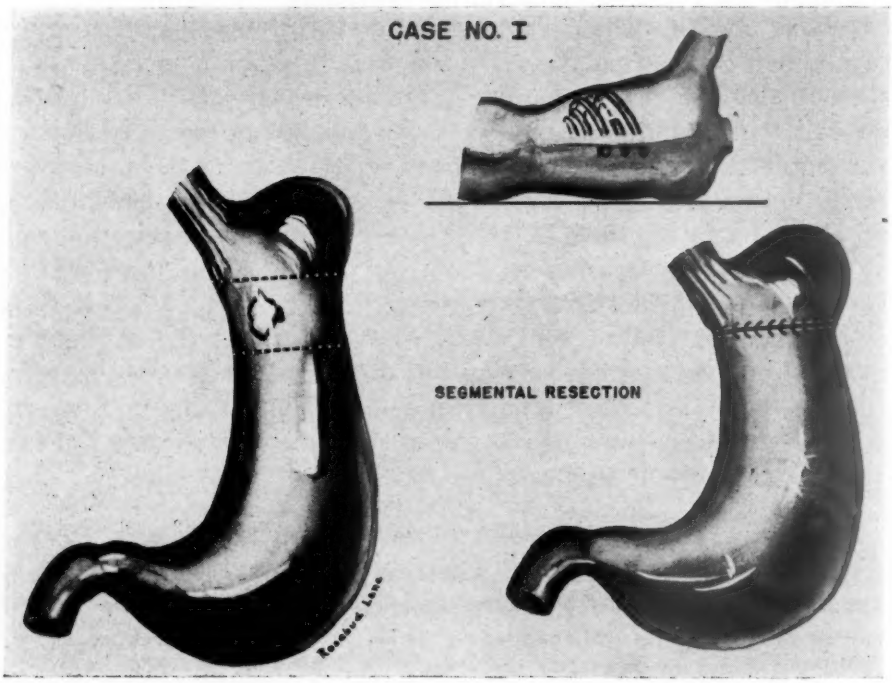
ILLUSTRATIVE CASE REPORTS

CASE 1 (Fig. 2).—This case is an example of a high-lying gastric ulcer which failed to heal under appropriate medical management.

This 56-year-old woman was admitted to the hospital for surgical treatment of a gastric ulcer which had failed to heal after three weeks of rigid medical management. Repeated gastric analyses were never over 5° for free hydrochloric acid. A transthoracic approach through the bed of the ninth rib on the left was used. There was a large gastric ulcer situated high on the lesser curvature within 2.5 cm. of the right border of the esophagus. Leaving the distal portion intact, the stomach was transected well below the ulcer. The transected stomach, dissected off the pancreas, was reflected upward and was again divided at the right border of the esophagus. The pathologist reported a benign lesion. The cuff of stomach which was preserved above was anastomosed to the intact lower portion. The

A. B.





C.

Fig. 2 (Case 1).—*A*, Preoperative roentgenogram depicting a large ulcer crater high on the lesser curvature. *B*, Postoperative roentgenogram one year later, illustrating functioning anastomosis between the remnant of the cardia and the distal gastric segment. *C*, Illustrated operative approach. Transthoracic segmental gastrectomy through the bed of the ninth rib on the left with anastomosis of the cardia to the distal gastric stomach. The ulcer in this instance is within 2.5cm. of the esophagus and would almost necessarily require total gastrectomy through the abdominal route.

operation was terminated, and the patient made an uneventful recovery. Subsequent x-ray examinations revealed no evidence of recurrence. The patient has remained asymptomatic since operation two years ago.

CASE 2 (Fig. 3).—This patient, with an ulcerating, bleeding leiomyoma, was treated by wedge resection.

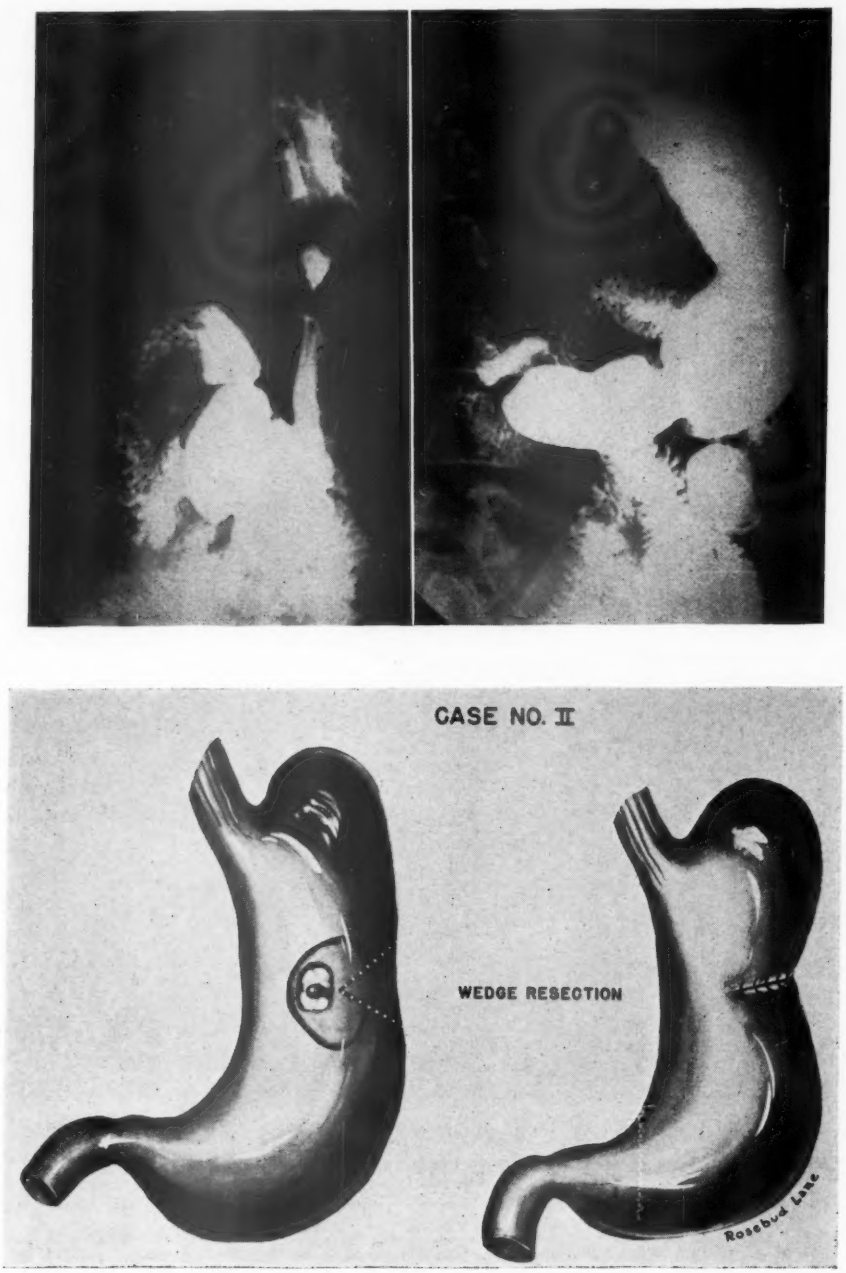
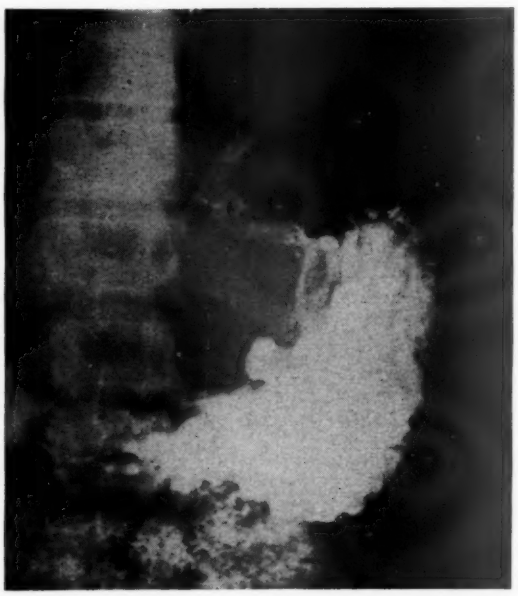
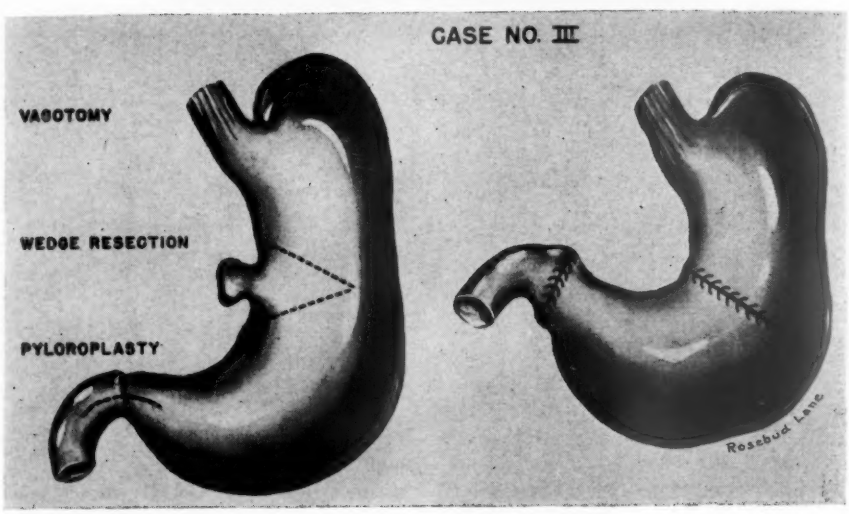


Fig. 3 (Case 2).—*A*, Preoperative roentgenogram illustrating large ulcer crater in the mid-portion of the stomach. *B*, Postoperative roentgenogram showing a well-functioning, almost intact stomach two years after operation. A defect in the region of the lesser curvature is scarcely discernible. *C*, Drawing of operative procedure showing wedge resection of the greater curvature to include the pedicle of an ulcerating benign tumor.

This 52-year-old woman was admitted for treatment of an acute gastric hemorrhage. Hemoglobin was 8.1 Gm. Roentgenograms revealed a large posterior gastric ulcer at the junction of the middle with the upper one-third of the stomach. Operation was carried out because of persistent hemorrhage, after twenty-three consecutive blood transfusions. At operation

A.





B.

Fig. 4 (Case 3).—*A*, Preoperative roentgenogram illustrating a large ulcer on the lesser curvature of the stomach. *B*, Operative procedure illustrating vagotomy, wedge resection, and pyloroplasty with preservation of the major portion of the stomach.

through the abdominal route a globular, mobile, dense 8 cm. tumor mass could be palpated within the lumen of the stomach. It appeared to be attached by a pedicle to the greater curvature. The lumen was opened and a benign-appearing tumor with a large ulcer crater was found with signs of acute bleeding. It was apparent that a shallow wedge resection of the greater curvature of the stomach would easily include the pedicle of the tumor. This

was done, and the pathologic diagnosis was benign ulcerating leiomyoma. The patient made an excellent recovery and has remained well since. A recent check-up examination, twenty-three months after surgery, shows a well-functioning stomach without recurrent ulcer.

Comment.—In these two instances a conservative resection has been apparently as effective in the treatment of the lesions as a high subtotal resection. In neither of the foregoing instances was vagus nerve resection performed.

CASE 3 (Fig. 4).—This patient, with an ulcerating mid-lesser curvature lesion of the stomach, was treated by vagotomy, wedge resection, and pyloroplasty.

This 55-year-old man had a four months' history of rather severe epigastric pain which was not relieved by medical treatment. The fasting free hydrochloric acid was normal (25°). Roentgenograms revealed a large ulcer of the lesser curvature. A vagotomy, wedge resection, and pyloroplasty were done. The ulcer was reported as benign by the pathologist. It is now twenty-six months since operation, and the patient has remained well except for occasional bouts of diarrhea.

CASE 4 (Fig. 5).—This patient, with a prepyloric ulcer, was treated by segmental resection (Billroth I) plus vagotomy.

This 55-year-old man was admitted to the hospital July 1, 1948, with a thirteen-year history of epigastric pain. At operation a 1 cm. prepyloric ulcer was found on the lesser curvature. Segmental resection (Billroth I) and vagotomy were performed. The patient was asymptomatic for twenty-nine months, when he began having dysphagia. X-ray examination and esophagoscopy revealed a mass in the esophagus at the level of the aortic arch. An esophagectomy was done for a primary squamous-cell carcinoma. The stomach was anastomosed to the remaining esophagus above the level of the arch. No evidence of recurrence of the gastric ulcer was found at operation.

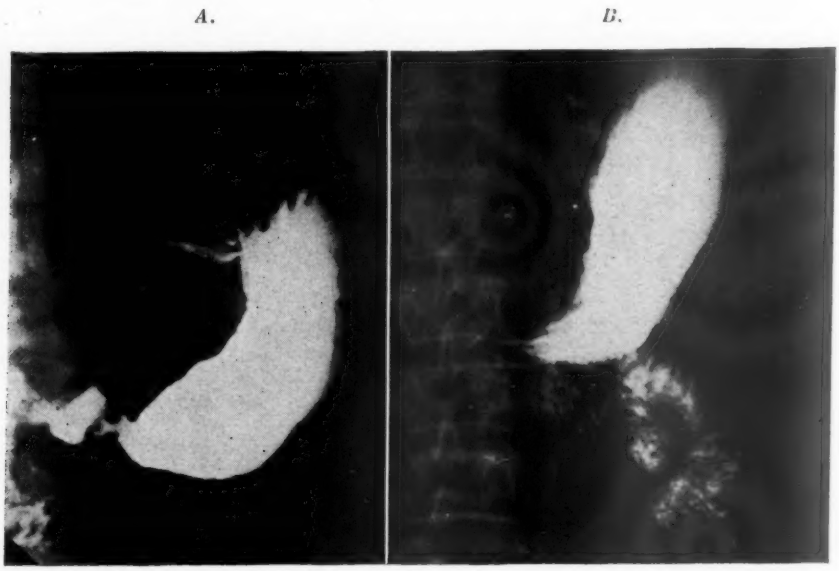
Comment.—Had a subtotal gastrectomy been performed previously for the benign gastric ulcer, it would have been necessary to attempt the use of the jejunum for the esophageal anastomosis rather than the stomach.

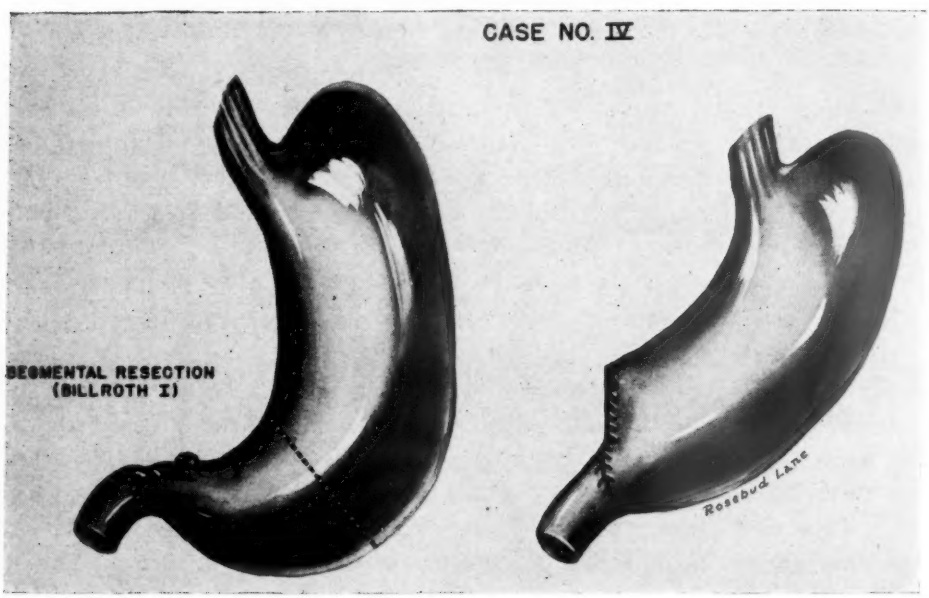
CLINICAL RESULTS

Follow-up studies from two to thirty months have been carried out in all of the thirty-two patients; fourteen have been followed for eighteen months or longer. Wherever possible, these studies have been carried out by having the patient readmitted to the hospital for gastrointestinal x-ray examination, gastroscopic examination, gastric analysis, and clinical evaluation. One patient died of an unrelated cause approximately four months after operation.

There are two patients in whom the results are considered unsatisfactory; both patients had a wedge resection combined with pyloroplasty without vagotomy. Gastroscopic examination in one of them (two months after operation) showed evidence of a shallow recurrent ulceration although extensive x-ray studies were negative. It is entirely possible that the gastroscopic findings are related to impaired union of the mucous membrane as the result of inaccurate suture. This view is supported by the fact that three weeks later a second gastroscopic examination failed to reveal any evidence of ulcer. The other unsatisfactory result has occurred in a patient with a strong emotional background. Although there is no evidence of ulcer by roentgenologic or gastroscopic examination, the symptoms continue. The red blood count is normal, and gastric acids are 0°.

There are also two patients who show roentgenologic evidence of delayed emptying although there are no objective or subjective signs of ulcer. Both of these patients had a wedge resection of the lesser curvature and vagotomy without a gastric drainage procedure. They consider their clinical result to be satisfactory although there are mild troublesome symptoms related to the delayed emptying.





C.

Fig. 5 (Case 4).—*A*, Preoperative roentgenogram of prepyloric ulcer. *B*, Postoperative roentgenogram illustrating an essentially normal stomach. *C*, Diagrammatic representation of segmental resection of the lower segment of the stomach, as in Billroth I.

TABLE III

CASE NO.	SEX	AGE (YEARS)	TYPE OF RESECTION	POST-OPERATIVE FOLLOW-UP	VAGOTOMY	TYPE OF DRAINAGE	RESULTS
5	M	46	Wedge	29 mo.	Yes	None	No evidence of ulcer by x-ray or gastroscopic examination; fasting acid 0°; asymptomatic
6	M	64	Wedge	29 mo.	Yes	Gastroenterostomy	No evidence of ulcer by x-ray examination; refused gastroscopic examination; asymptomatic; fasting acid 0°
7	M	36	Wedge	29 mo.	Yes	None	At 1 year follow-up, no evidence of ulcer by x-ray; fasting acid 2°; recent follow-up by letter: patient stated that he felt fine except for occasional mild diarrhea, was working hard, and "unable to leave work now for hospital examination"
8	M	54	Wedge	29 mo.	Yes	None	Some symptoms associated with gastric retention; delayed emptying by x-ray; acid 15°; no evidence of ulcer by x-ray or gastroscopic examination
9	M	51	Wedge	26 mo.	Yes	None	No evidence of ulcer by x-ray or gastroscopic examination; "occasional belching," feels fine otherwise; delayed gastric emptying by x-ray; fasting acid 2°
10	M	47	Wedge	24 mo.	Yes	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; fasting acids 0°; much relief since operation although patient occasionally has mild epigastric distress
11	M	37	Wedge	22 mo.	Yes	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; fasting acid 7°; no complaints
12	M	53	Wedge	19 mo.	Yes	Pyloroplasty	No evidence of ulcer by x-ray; Fasting acid 0°; no complaints
13	M	63	Wedge	18 mo.	Yes	Pyloroplasty	Hospitalized elsewhere for cardiac failure; report from physician reveals no ulcer symptoms
14	M	48	Wedge	18 mo.	Yes	Pyloroplasty	Episodes of diarrhea for first year following surgery, did not interfere with patient's work; fasting acid 0°; patient feels fine
15	M	41	Wedge	16 mo.	Yes	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; no complaints
16	M	53	Wedge	1 yr.	Yes	Gastroenterostomy	No evidence of ulcer by x-ray examination; fasting acid 0°; asymptomatic
17	M	52	Wedge	1 yr.	No	Pyloroplasty	Patient feels perfectly well; was admitted for postoperative study but said felt fine and didn't want to stay for evaluation

TABLE III—CONT'D

CASE NO.	SEX	AGE (YEARS)	TYPE OF RESECTION	POST-OPERATIVE FOLLOW-UP	VAGOTOMY	TYPE OF DRAINAGE	RESULTS
18	M	64	Wedge	1 yr.	No	Pyloroplasty	Patient asymptomatic, "eats everything," is working
19	M	54	Billroth I	10 mo.	Yes	None	No evidence of ulcer by x-ray examination; fasting acid 0°, asymptomatic
20	M	52	Wedge	9 mo.	No	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; fasting acid 0°; no complaints
21	M	31	Wedge	9 mo.	Yes	Pyloroplasty	Patient symptom-free except for occasional bout of diarrhea; stated that "this operation is the most wonderful thing that has ever happened to me"
22	M	59	Wedge	8 mo.	No	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; fasting acid 0°; no complaints
23	M	45	Wedge	7 mo.	No	Pyloroplasty	No evidence of ulcer by x-ray or gastroscopic examination; fasting acid 11°; asymptomatic
24	M	49	Wedge	7 mo.	No	Pyloroplasty	Patient's symptoms have continued since surgery even though the fasting acids are 0°, R.B.C. 5.13 million, and there is no evidence of ulcer by x-ray or gastroscopic examination; classified as a failure
25	M	49	Wedge	6 mo.	Yes	None	Asymptomatic even though x-ray revealed moderate gastric retention at 6 hours; fasting acid 0°
26	M	56	Wedge	6 mo.	Yes	Pyloroplasty	Patient's only complaint is inability to regain preoperative weight; working full time
27	M	59	Wedge	6 mo.	Yes	Gastroenterostomy	No evidence of ulcer by x-ray or gastroscopic examination; asymptomatic
28	M	47	Wedge	4 mo.	No	Pyloroplasty	Ulcer symptoms recurrent postoperatively; superficial ulceration seen on lesser curvature by gastroscopic examination; acids 0°; after 3 weeks of medical treatment he was re-gastroscoped and ulceration had healed; classified as a failure
29	M	35	Wedge	3 mo.	No	Pyloroplasty	Has no complaints, working full time
30	M	62	Wedge	3 mo.	No	Pyloroplasty	Patient died 3 months after surgery from a severe fulminating hepatitis
31	M	37	Wedge	2 mo.	Yes	Pyloroplasty	Patient has felt well since surgery; operation too recent for re-study
32	M	56	Wedge	1 mo.	Yes	Gastroenterostomy	Operation too recent for re-study; patient has no complaints

It is known that wedge resection alone is capable of producing alterations in gastric emptying. This may be due to interference with the origin and conduction of peristaltic pathways and/or interruption of vagus innervation. Irrespective of vagotomy, it would appear that gastroenterostomy or pyloroplasty should be employed when the lesser curvature is resected.

Results of operation are considered to be entirely satisfactory except for the previously mentioned cases. A summary of the clinical data is given in Table III.

It is noteworthy that the unsatisfactory results occurred in those patients in whom vagus resection was omitted. This suggests that the vagus operation as an adjunct to segmental resection and pyloroplasty affords some protection against the gastric ulcer diathesis, although definite conclusions cannot be drawn from this small series of cases. They will be followed closely for future developments. Certainly this procedure at the present time must be considered in the early investigative phase.

The most significant clinical consideration in the treatment of gastric ulcer is the presence or absence of malignancy. This approach to the problem provides the solution to this question.

SUMMARY AND CONCLUSIONS

1. A series of thirty-two patients with benign gastric ulcer is presented.

2. All of these patients have been treated by some type of conservative segmental or wedge resection. Frozen sections of the specimen were made at the time of operation. There have been no operative deaths.

3. Approximately two-thirds of the patients have had vagotomies in addition to conservative resection. In slightly over two-thirds of the cases a supplementary gastric drainage procedure has been done as well. The most satisfactory immediate results appear to be in this group of wedge resections plus vagotomy combined with a gastric drainage procedure.

4. One patient suffered from a questionable recurrent ulceration which healed subsequently. Another patient died from an unrelated cause. A third patient, although showing no evidence of ulcer by x-ray or gastroscopic examination, has a poor subjective result. The remaining twenty-nine patients, followed from two to thirty months, are living and free from ulcer symptoms. Most of them are enthusiastic over the results of their operation. There are two patients who have mild, troublesome symptoms related to delayed emptying.

5. One of the primary considerations in the surgical treatment of gastric ulcer is the presence or absence of malignancy. This conservative approach offers a solution to the problem with an opportunity to limit logically the extent of the operation in the presence of a benign lesion—and to extend logically the scope of operation with appropriate extensive resection of the omenta and lymphatics, and wide excision of gastric tissue in the presence of malignancy.

REFERENCES

1. Walton, A. J.: in Maingot, Rodney: Abdominal Operations, Vol. 1, New York, 1940, D. Appleton-Century Company, Inc., p. 308.

2. Eusterman, G. B., Balfour, D. C., and members of Staff of the Mayo Clinic and Mayo Foundation: The Stomach and Duodenum, Philadelphia, 1935, W. B. Saunders Company.
3. French, J. D., von Amerongen, F. K., and Raney, R. B.: Gastrointestinal Hemorrhage and Ulceration Associated With Intracranial Lesions: A Report of 14 Cases, J. Neurosurg. To be published.
4. Hart, C.: Betrachtungen über die Entstehung des peptischen Magen und Quoelffinger darmgeschwueres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 31: 350-80, 1918-1919.
5. Berg, M.: Experimental Peptic Ulcer by Vasomotor Episodes (Pitressin Episodes) and Autonomic Disturbances, Arch. Path. 33: 636, 1942.
6. Light, R. U., Bishop, C. C., and Kendall, L. G.: Production of Gastric Lesions in Rabbits by Injection of Small Amounts of Pilocarpine Into Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. 45: 227, 1932.
7. Necheles, H., and Masur, W.: Gastrointestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin, Am. J. Digest. Dis. 6: 389, 1939.
8. Nedzel, A. J.: Experimental Gastric Ulcer (Pitressin Episodes), Arch. Path. 26: 988, 1938.
9. Nedzel, A. J.: Experimental Production of Gastric Ulcers in Dogs by Inducing Vascular Spasm With Pitressin, Am. J. Digest. Dis. 10: 283, 1943.
10. Tedeschi, C. G.: Gastric Mucosal Lesions in Rats Submitted to Head Trauma, Proc. Soc. Exper. Biol. & Med. 57: 268, 1944.
11. Wang, S. C., Clark, G., Dey, F. L., and Ranson, S. W.: Further Study on Gastrointestinal Motility Following Stimulation of Hypothalamus, Am. J. Physiol. 130: 81, 1940.

DISCUSSION

DR. WILLIAM A. COOPER.—At the New York Hospital over the years we have followed the policy of resecting gastric ulcers, as most of us have, but as time has gone on we have collected a small number of patients on whom for one reason or another resection has been either impossible or thought to be unwise. There are sixteen such patients, and I had occasion not long ago to go over them all. They have been followed from five to fifteen years. All of those sixteen patients were treated by simple gastroenterostomy, and fifteen of the sixteen have had a perfect clinical result. I think that this should be mentioned as one of the old-fashioned conservative treatments of gastric ulcer that works.

DR. KEITH S. GRIMSON.—One should remember that reports of results of vagotomy alone for gastric ulcer have been poor. However, if one separates from the reported cases those in which an associated gastroenterostomy has been done, then results are encouraging. The procedure which Dr. Wilkins has reported, vagotomy with gastroenterostomy and with local resection of ulcer, does not run the chance of overlooking a malignancy. Certainly this technique gives one an opportunity to treat gastric ulcers individually by selecting the type of operation to be used. In instances of very extensive penetrating gastric ulcers with danger of injury to the pancreas, liver, or bile ducts if excised, we do have available a less radical procedure than subtotal or total gastric resection and might, at least occasionally, elect conservatism using vagotomy and gastroenterostomy alone and accepting a moderate risk of malignancy.

DR. FRANKLIN B. WILKINS (Closing).—I would like to re-emphasize one point and that is that we are not advocating at this time that vagotomy, wedge resection, and pyloroplasty replace subtotal resection as the treatment for all benign gastric ulcers. We do, however, think that the results have been sufficiently satisfactory with this combination that further study and follow-up is indicated, particularly in patients with ulcers located very high on the lesser curvature, to determine whether this procedure might be just as satisfactory or even more satisfactory than the subtotal resection that would be necessary in such cases.

Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS, FEB. 8-10, 1951, DURHAM, N. C.

F. A. SIMEONE, M.D., CLEVELAND, OHIO

THE twelfth annual meeting of the Society of University Surgeons was held in Durham, N. C., on Feb. 8, 9, and 10, 1951. The Society was guest of the Department of Surgery, Duke University School of Medicine. The scientific program was presented in Page Auditorium on the Duke University campus.

The meeting was opened by **Dr. Jean M. Stevenson**, president of the Society, and after welcoming remarks by **Dr. Wilburt C. Davison**, Dean of the Duke University School of Medicine, the first day was devoted to the presentation of papers by members of the medical school and hospital staffs. Brief abstracts of these papers are included in this section. The presentation of reports on current research was followed by a tour of the laboratories.

The second and third days of the meeting were devoted to a presentation of papers by members and guests of the Society. These are published in this issue of the JOURNAL. Abstracts of papers by members of the Duke University School of Medicine follow.

Comments on Surgery of the Autonomic Nervous System, Keith S. Grimson. "Total" sympathectomy for hypertension performed during eleven years has been accomplished with a 3.9 per cent mortality rate, an 86.4 per cent five-year survival, and maintained reduction of pressure to near normal in one-third of the 154 patients. Vagotomy-gastroenterostomy performed in 172 patients during six years has been accomplished with an 0.6 per cent mortality rate, subjectively satisfactory results in 71.9 and objectively satisfactory results in 94.8 per cent, the recurrence rate being 1.2 per cent. Transdiaphragmatic sympathectomy has effected good results in four and fair results in two patients with "aortitis obliterans." Celiac ganglionectomy has accomplished denervation of abdominal pain pathways in 16 patients. Results of use of Urecholine for megacolon and Banthine for ulcer or hyperhidrosis will be summarized.

The Use of Positron-Emitting Radioisotopes for the Localization of Brain Tumors, Frank Wrenn. To locate accurately a point source or delimit an extended source of radioactivity such as radioisotopes concentrated in a brain tumor, the system employed must be capable of sharply resolving the limits of greater concentration with reference to a suitable coordinate system. This requires that either the detector or the radiation be directional and that scattering within the head mass be minimzed.

On the basis of physical considerations it appears that more accurate source delimitation would be possible through the use of a technique of coincidence scintillation counting of the annhilation quanta of positron emitters, a system in which direction is inherent in the radiation.

Physical experiments supporting this original hypothesis will be described. Preliminary work demonstrating that clinical implementation may be obtained through the use of copper^{64} sulfophthalocyanine will be described. Clinical trials of the technique are under way.

The Response of the Heart to Vagal Stimulation in Hypercapnia and Hypoxia, W. C. Sealy, W. G. Young, Jerome Harris, and **Arnold Botwin.** The various factors leading to sudden cardiac arrest during operations are poorly understood. The possible relation of hypercapnia and vagal stimulation to this accident was studied. The duration of asystole from continuous faradic stimulation of cervical vagus was used as an indication

of the effect on the heart of hypercapnia and hypoxia alone and when combined. It was found that hypercapnia markedly enhances the effect of vagal stimulation on the heart, while, on the other hand, hypoxia diminishes this effect even when combined with hypercapnia. The role of the combination of hypercapnia and vagal stimulation in the initiation of cardiac arrest is discussed.

Correlation of Blood pH and Shock in Thoracoplasties, James D. Moody, and **C. Keith Lyons.** The problem of acidosis during thoracic surgery has been well emphasized by the work of Beecher and others. It has been suggested that paradoxical respiration is the predominant factor in the increase in alveolar carbon dioxide tension, and lowering of blood pH, thus predisposing to shock. Preliminary observations during operation on a group of five patients undergoing thoracoplasties showed distinct lowering of blood pH witih the patient in the lateral position and having some degree of respiratory paradox. Immediate postoperative studies in the same patients with a comparable degree of paradox but in a supine position showed no significant change in blood pH or blood pressure. The factor of position thus seems to be a major one, and warrants further study.

Removal of Internal Mammary Lymphatics in Carcinoma of the Breast (Preliminary Report), Clarence E. Gardner, Jr., George H. McSwain, and **James D. Moody.** An internal mammary lymph node is removed during each radical mastectomy for carcinoma. If found by immediate microscopic study to contain carcinoma the first to fifth costal cartilagers are removed, the clavicle divided, and internal mammary vessels and lymphatics are removed. A radical dissection of the innominate and subclavian vein in continuity with the usual axillary dissection is also done.

The series is small. At the present time 25 per cent of cases selected for radical mastectomy have carcinoma in the internal mammary nodes. Although the operation described increases postoperative discomfort and deformity it is hoped that it will salvage some of the patients otherwise doomed to recurrence.

Observations on the Complete Reversal of the Circulation in the Hind Limb of the Dog, T. B. Ferguson, W. C. Sealy, W. G. Young, and **R. A. Gowdy.** Observations were made in ten dogs on the effects produced by cross-cannulating the femoral vessels so that arterial blood was delivered to the extremity by the veins and returned by the arteries. Pressure and volume flow measurements were recorded with the collateral circulation intact and with it occluded. These observations showed that arterial blood directed into venous systems with patent communicating channels and competent valves will by-pass the capillary bed and be shunted back toward the heart. Arterial blood directed into venous systems with incompetent valves and with communicating veins occluded results in diminshed blood flow and marked engorgement and edema.

Influence of Vagus Nerves in Experimental Pancreatitis, William W. Shingleton, W. G. Anlyan, and **Frederick Glass.** Previous studies by the authors have revealed that patients following vagotomy show a subnormal output of pancreatic enzymes with no response to injected secretin. Furthermore, Banthine, a vagal blocking agent, likewise prevents the normal pancreatic response to injected secretin.

Experimental pancreatitis has been produced in dogs by ligation of the pancreatic duct with injection of secretion and pilocarpine. Daily amylase blood determinations and pathologic sections of the pancreas were made and compared with similar studies in a group of animals that received Banthine in the postoperative period. It appears that Banthine is effective in the prevention of, and effects resolution in, the pancreatitis produced in this manner.

The Effects of New Drugs on the Circulation in Patients With Hypertension and Peripheral Vascular Disease, John R. Emlet and **Keith S. Grimson.** The newer autonomic blocking drugs affecting circulation include agents which interrupt ganglionic transmission, those which block the sympathetic (adrenolytic), and those which selectively block parasympathetic nerve transmission. Experiments with SC 1950, parenterally effective, and

hexamethonium bromide (C6), orally effective, demonstrate that they affect sympathetic and parasympathetic alike. The possible role of the latter in hypertension is determined by clinical trial. The sympatholytic drug, Regitine (C-7337), has aided patients with Raynaud's disease but has been of limited value in other peripheral vascular disorders and in hypertension. It is of value in diagnosis and operative management of patients with pheochromocytoma. Selectively parasympatholytic agents have atropine-like and no sympatholytic action in moderate doses. In larger doses they effect ganglionic blockade with resultant tachycardia and hypotension.

A Correlation Between the Intrinsic Muscle Mechanism of the Hand and Deformities of the Hand, J. Leonard Goldner. Physiologic function of the hand depends on coordination between the intact intrinsic muscle mechanism and the extrinsic muscles. Injury to any part of this system results in deformity. Trauma to the central slip of the extensor tendon, the laterial bands, or the main dorsal hood leaves an imperfect digit. Ischemic contracture of the intrinsic muscles, burn contracture of the dorsal fascia, or contracture of the lateral bands leaves typical changes in the hand. These contractures, as well as paralysis due to nerve injury, predispose to functional loss and irreversible deformity unless surgery supplemented by active corrective splinting is done.

An Immunological Study of Hemolytic Transfusion Reactions, Ivan W. Brown, Jr. The vast majority of hemolytic transfusion reactions are still due to incompatability of the ABO blood groups as the result of human error.

However, with the great increase in blood transfusion, particularly repeated transfusions, there are increasing numbers of hemolytic reactions due to one or more of the weaker blood group antigens such as c (Hr'), K (Kell), Fy^a (Duffy), and S. While these reactions are often subtle, they also may be fatal. Unfortunately, the sensitization by these weaker antigens is not always detected unless cross-matching procedures based on new immunologic principles are employed. Immunologic data on a number of these reactions are presented.

A Method of Skin Preservation—A Preliminary Report, R. L. A. Keeley, Alphonse C. Gomez, and **Ivan W. Brown, Jr.** This method consists in the ultrarapid cooling of split-thickness skin which has been previously dehydrated in ethylene glycol for at least 30 seconds.

Cooling velocities of several hundred degrees Centigrade per second are attained by plunging the dehydrated tissues into liquid nitrogen. Thus the zone of crystallization and cell death is avoided.

It is proposed that the amorphous state of vitrification, once attained, may be maintained by storing the tissue at -18° C. or lower and that by this procedure skin may be preserved for extended periods of time.

Autogenous dog skin preserved forty-five days then grafted has survived normally.

Antibiotic Neuritis: Changes in the Cat Sciatic Nerve Induced by Penicillin and Streptomycin, Thomas Ray Broadbent, Jerome Javer, and **Barnes Woodhall.** The reaction of peripheral nerve tissue to penicillin, its vehicles, and to dihydrostreptomycin has been studied in the cat. The clinical syndrome of penicillin-induced peripheral nerve paralysis has been reported by this laboratory.

Sesame and peanut oil produced a marked cellular response and fibroblastic proliferation. When sodium, potassium, or calcium penicillin were added to the oils both reactions were intensified and axonal degeneration was noted. The latter was particularly marked when the substance was injected subepineurally or intrafasicularly. Vehicles other than the oils produced little and, in some instances, no change.

Dihydrostreptomycin produced a similar but more marked response.

Studies on the Pathogenesis of Spontaneous Bacteremia and Valvular Endocarditis in Dogs With Peripheral Arteriovenous Fistulas, R. A. Gowdy, G. P. Kerby, S. P. Martin, and **W. C. Sealy.** It has been noted by Lillehei and associates that large arteriovenous

fistulas in dogs are frequently accompanied by bacterial endocarditis. In an attempt to explain the pathogenesis of these findings, animals with fistulas large enough to cause heart failure and death within twenty-four hours were studied and in all instances were found to have valvular edema and subendocardial hemorrhages. In a second group of animals, the effect of smaller arteriovenous fistulas on the extraction rate of infused bacteria was studied. In one acute animal and in two chronic animals with spontaneous bacteremias, the ability of the dogs to extract infused bacteria was normal.

Clinical Aspects of Oximetry, C. R. Stephen. The oximeter incorporates a photoelectric technique which allows accurate estimation from minute to minute of the arterial oxygen saturation of the patient. Its employment during operation permits recognition of a trend toward anoxia before such is recognized clinically by cyanosis. Examples are shown to demonstrate its importance both to the surgeon and the anesthetist.

Immunological Reactions in Cancer; I The Production in Rabbits of Specific Hemagglutinins to Some Human Cancers and Normal Tissues, William G. Anlyan, William W. Shingleton, and **Frank H. Campbell.** The voluminous literature on tumor immunity is based mainly on work done with experimental animal tumors; reports on the immunologic properties of human tumors are scanty.

The authors have initiated a study of the antigenicity of some human cancers and parallel normal organs removed at operation and preserved in the frozen state. The tissues incorporated with Freund's adjuvants were injected intramuscularly and intraperitoneally into rabbits.

At regular intervals the rabbit sera were tested by a modification of the Smith-Scott tuberculosis hemagglutination test for the development of specific hemagglutinins. The latter were detectable in low titers in the majority of the rabbits.

New Method of Epithelial Tube Formation, E. P. Alyea and **Sam S. Ambrose, Jr.** Epithelial islands were made in the abdomens of dogs, and from these epithelial tubes formed completely within a period of nine days. Various sutures were used; various thicknesses of the epithelial islands were made. Polyethylene tubing was also used to see whether the tubes would form more perfectly. Sections were taken at intervals to see just when the epithelization was complete. Tests were made to see whether stricture formation took place as long as three months after operation.

This method has been applied clinically to the hypospadias patient with considerable success.

The Effects of New Drugs on Gastrointestinal Dysfunctions and Disorders, Benjamin H. Flowe and **Keith S. Grimson.** Autonomic drugs affecting the gastrointestinal tract in general fall into three types—anticholinergic, cholinergic, and ganglionic blocking. The actions of these various drugs will be presented. The anticholineric drugs, such as Banthine, have greatest usefulness because of their selective blockade of the parasympathetic nervous system. Resulting decrease in gastrointestinal motility and secretions led to clinical trial for peptic ulcer. Of the cholinergic drugs, Urecholine has been found most effective in treatment of postvagotomy retention, megacolon, and other disorders. The ganglionic blocking drugs, Etamon, SC-1950, and hexamethonium bromide, block both sympathetic and parasympathetic impulses. These agents decrease gastrointestinal motility and secretions but because of cardiovascular effects such as postural hypotension are of limited usefulness in gastrointestinal disorders.

The Virus of Erythromyeloblastic Leucosis, J. W. Beard, Dorothy Beard, Edward A. Eckert, T. Z. Csaky, and **D. G. Sharp.** Avian erythromyeloblastic leucosis is a virus-induced neoplastic disease of fowls transmissible experimentally by transfer of filtered plasma to susceptible chicks. By means of ultracentrifugal procedures, a particulate component which appears to be the causative virus has been isolated from the filtered plasma. Electron micrographic studies have been made of the morphology of the sperm-shaped particles. Such particles have not been found in the plasma of unaffected birds, and serologic studies have failed to reveal a relationship to other avian viruses.

Effects of Banthine, Atropine, and Dibutoline on Gastric Secretion and Motility, C. Keith Lyons and **Keith S. Grimson.** When injected intravenously or intramuscularly atropine, Dibutoline, and Banthine each depress gastric motility and secretions. Action of atropine and Dibutoline was not consistent or prolonged. That of Banthine was almost consistent and lasted two to four hours. By oral administration Dibutoline Ethosulfate was ineffective, atropine poorly and irregularly effective, and only Banthine produced consistent effects lasting several hours. In some patients Banthine orally or parenterally altered the hypersecretion response to insulin-induced hypoglycemia. Results seem to indicate that of the drugs studied Banthine is the more effective agent in reducing hypermotility and hyperacidity, effects which should aid treatment of peptic ulcer.

The Correction of Ankylosis of the Jaw, Kenneth L. Pickrell and **Benjamin F. Edwards.** One of the most interesting phases of reconstructive surgery may be found in the correction of ankylosis of the temporomandibular joint and the concomitant deformities of the face. While many individuals readily compensate for physical or physiologic impairments, there is no method of compensation possible when one is unable to open or close the mouth. Since the sequalae of injury and disease are so disabling and so deforming, the general surgeon as well as the plastic surgeon is frequently called upon to reconstruct the jaw—to restore or preserve function, and to improve the appearance of the face. It is of importance then to have at our command a simple operation which will not jeopardize the function of the facial nerve, and the operation must restore function.

The operation described is performed through a concealed submandibular incision just behind the angle of the jaw. The masseter muscle is split in half in the direction of its fibers. The insertion of the posterior one-third of the masseter muscle is severed at the angle of the mandible. This will facilitate exposure of the entire joint to determine whether the condyle alone is involved or whether the coronoid is also fixed. When in doubt, the neck of the condyle is sectioned first, using a Gigli saw, rongeur, or osteotome. If, after resecting the condylar neck, motion of the joint is still restricted, then the coronoid is resected also. One centimeter or more of bone is removed. The site of the ostectomy should be above the entrance of the inferior alveolar nerve and vessels. The free masseter muscle flap is then interpolated into the space created by the ostectomy and tucked behind the sectioned ramus. One or several sutures are used to unite the flap of masseter with the underlying internal pterygoid muscle. The inner position of this muscle mass will prevent union of the cut bone surfaces and will act as a shock absorber for the reconstructed jaw.

The procedure described has been used on twelve consecutive patients, eight with unilateral and four with bilateral ankylosis.

Effects of Veriloid Intravenously in Dogs and Intravenously and Orally in Patients, R. G. Connar, J. R. Emlet and **K. S. Grimson.** Veriloid was administered intravenously to ten anesthetized dogs and to four unanesthetized neurogenic hypertensive dogs producing an effective fall in blood pressure and reduction of pulse rate in each. In sixteen hypertensive patients single intravenous injections of Veriloid effected a reduction of blood pressure and slowing of pulse rate. A continuous intravenous infusion of Veriloid was administered to six hypertensive patients for periods ranging from three to seventeen days. Reduction of blood pressure to desired levels was brought about by varying the rate of infusion. Results of oral Veriloid in fifteen ambulatory hypertensive patients were not impressive.

Method of Recording Intracranial Arterial Pressure, Guy L. Odom and **Bryon Bloor.** A method of recording intracranial arterial pressure to determine the adequacy of collateral circulation through the circle of Willis is described. A Sanborn electric manometer with an amplified recorder is used with a No. 28 needle inserted into the vessel and connected to the manometer by a flexible lead tube. With the needle in a cortical arteriovenous angioma, a drop in pressure of 40 per cent was recorded from occlusion of the

common carotid artery, 37 per cent from the internal carotid artery in the neck, and 30 per cent from a branch of the middle cerebral artery which was the main feeder of the angioma.

The dangers associated with carotid ligation are discussed and it is suggested that this method be used to decrease the complications associated with intracranial approach to berry aneuryms and angiomas.

Multiple Myeloma; III. Effect of Urethane Therapy on Plasma Cell Growth, Abnormal Serum Protein Components, and Bence Jones Proteinuria, R. Wayne Rundles, M. L. Dillon, and **Edith S. Dillon.** A study of eleven patients shows plasma cell growth is inhibited by urethane in multiple myeloma. Abnormal serum protein components, even those generally found not to represent Bence Jones proteinemia, are reduced or may virtually disappear. This change parallels the reduction or disappearance of Bence Jones proteinuria. During prolonged continuous administration of urethane myeloma cells may become dependent on the chemical.

Use of the Anal Sphincters to Sustain Fecal and Urinary Control in Neovesical Formation, S. S. Ambrose, Jr. A preliminary report is presented of the re-investigation of a method of urinary stream diversion so that continence of separate urinary and fecal streams is maintained by the anal sphincters. The colon is divided above the cephalic hemorrhoidal artery and the undisturbed rectum is excluded for future transplantation of the ureters. A perineal sigmoidostomy is formed by pulling the colon through the pelvic floor anterior to the rectum and between the anal sphincters and anal muscularis. Three dogs on which this was performed maintained fecal continence for nine months, and the rectal pouch was continent of fluid and completely emptied on overdistention.

An Experimental Method for the Evaluation of Contrast Media Used in Cerebral Angiography, Byron M. Bloor, Frank R. Wrenn, Jr., and **George J. Hayes.** Experimental studies of contrast media have followed two avenues: (1) histopathologic studies, which for the most part have given negative results, and (2) the physiologic approach of Broman using the dye indicator technique to demonstrate increased permeability of the cerebral vessels. The present method of study combines the dye indicator technique with concomitant electroencephalography in an effort to obtain evidence of more subtle changes in cerebral physiology as well as correlative data.

Adult rabbits were used since they receive a significant volume of blood to the cerebral hemisphere through the internal carotid artery. The tetra-sulfonic acid of copper phthalocyanine was used as the vital dye in these experiments. Continuous electroencephalograms were obtained during the injection of various contrast media through the internal carotid artery.

The contrast media tested appear capable of altering both cerebral vascular permeability and cerebral electroactivity when injected within the cerebral circulation.

Renal Dynamics in Coarctation of the Aorta, W. G. Young, W. C. Sealy, Jerome Harris, and **William DeMaria.** In coarctation of the aorta diastolic hypertension occurs above and below the stricture and has been considered to be the result of renal ischemia. Renal clearance studies were done, both in patients before and after resection of the stricture and in dogs before and after coarctation was induced. Studies on patients showed only an immediate postoperative increase in the renal blood flow and filtration rate followed in two to three months by a return to the preoperative level. In dogs there was no significant alteration in the renal clearance studies, nor was there any correlation of the blood pressure changes and renal clearances. It is considered that some factor other than renal ischemia is responsible for the hypertension on coarctation of the aorta.